Manufacturer Submission

To

The National Institute for Health and Clinical Excellence

By

GlaxoSmithKline UK

Single technology appraisal of lapatinib for the treatment of women with previously treated advanced or metastatic ERbB2- (HER2) over-expressing breast cancer

17 April 2007

Glossary of Key Abbreviations

Abbreviation	Full name
AE	Adverse event
bd	Twice daily
BNF	British National Formulary
CBR	Clinical benefit rate
CEAC	Cost-effectiveness acceptability curves
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DES	Discrete event simulation
DLTs	Dose limiting toxicities
DOH	Department of Health
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Co-operative Oncology Group Performance Status
EGFR	Epidermal growth factor receptor 1 (also known as ErbB1 or HER1)
EMEA	European Medicines Evaluation Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	Euro QOL questionnaire
ER+/-	Oestrogen receptor positive/negative
ErbB1	Epidermal growth factor receptor (also known as HER1)
ErbB2	Alternative name for HER2
ERG	Evidence Review Group
EU	European Union
FACT-B	Functional Assessment of Cancer Therapy-Breast
FACT-G	Functional Assessment of Cancer Therapy-General
FISH	Fluorescence *in situ* hybridisation
GP	General practitioner
GSK	GlaxoSmithKline
HER2	Human epidermal growth factor receptor 2 (also known as ErbB2; gene called neu)
HER2+	HER2-positive
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IMS	Intercontinental Marketing Services
IRC	Independent Radiological Review Committee
ITT	Intention to treat
IV	Intravenous
KPS	Karnofsky Performance Score
LOCF	Last-observation carried forward
LVEF	left ventricular ejection fraction
LY	Life year
MAA	Marketing authorisation application
mg or mg/m^2	Milligram or milligram per meter squared
mg or mg/m^2/d	Milligram or milligram per meter squared/day
Mg/kg	Milligram per kilogram
MUGA	MUltiple Gated Acquisition scan
NA	Not applicable
NCI	National Cancer Institute
NE	Not Evaluable
NE	North East (in the context of cost-effectiveness planes)
NR	Not recorded / reported
ORR	Overall response rate

OS	Overall survival
OTR	Optimally tolerated regimen
PD	Progressive disease
PFLY	Progression free life year
PPE	Palmar-Plantar Erythrodysaesthesia (also known as hand-foot syndrome)
PPLY	Post progression life year
PPS	Post progression survival
PR	Partial response
PR+/-	Progesterone receptor positive/negative
PS	Performance status
q21d	Every 21 days
q3w	Every 3 weeks
QALY	Quality adjusted life year
qw	Weekly
RCT	Randomised Controlled Trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Standard deviation
SD	Stable disease (in the context of assessing disease progression)
SE	Standard error
SE	South East (in the context of cost-effectiveness planes)
SG	Standard gamble
SmPC	Summary of product characteristics
TA	Technology appraisal
TOI	Trial Outcome Index
TTP	Time to progression

Acknowledgements

GlaxoSmithKline UK would like to thank the following external contributors for their help in developing and drafting the analyses presented in Sections 5, 6 and 7:

- Heron Evidence Development Ltd. (conducting systematic review and assistance with drafting Section 5)
- Policy Analysis Inc. (PAI, development of the core economic model, sensitivity analysis on adverse event costs)
- Sheffield School of Health and Related Research (ScHARR, customisation of economic model; budget impact analysis; assistance with drafting Sections 6 and 7)
- Oxford Outcomes (systematic review of cost-effectiveness literature and model validation)

1. Description of technology under assessment

1.1. Give the brand name, approved name and, where appropriate, therapeutic class.

Brand name: Tyverb™ (Note: Tyverb is currently the proposed brand name for lapatinib in Europe. Lapatinib is known as Tykerb® in the US and other non-European markets. It was also previously known as Tykerb in Europe but the name Tyverb was proposed in February 2007 in order to have a single name that was acceptable in all EU markets).

Approved name: Lapatinib ditosylate monohydrate (Note: The adopted International Non-proprietary Name (INN) is lapatinib).

Therapeutic class: Antineoplastic agent. ATC Code L01XE07 (Protein Kinase Inhibitors).

1.2. Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission?

If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates)

No. A Marketing Authorisation Application (MAA) was filed with the European Medicines Evaluation Agency (EMEA) on 4th October 2006 and is now under review via the Centralised procedure. It is estimated that a pan-European marketing authorisation will be received during Q3 2007.

1.3. What are the anticipated indication(s) in the UK?

The likely indication for lapatinib is:

Lapatinib/Tyverb, in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2) and who have received prior therapy including trastuzumab, an anthracycline and a taxane.

Note: The draft Summary of Product Characteristics (SmPC) in Appendix 9.1 is the version submitted to the EMEA with the MAA for lapatinib in October 2006. The SmPC currently being proposed by GlaxoSmithKline will be provided to NICE by the end of April once it has been re-submitted to the Committee for Medicinal Products for Human use (CHMP) for further review. The efficacy data presented in section 5 of the revised SmPC will reflect that reported in the lapatinib registration study (EGF100151) for the 03 April 2006 cut-off, as presented in Section 5 of this submission.

1.4. To what extent is the technology currently being used in the NHS for the proposed indication?

Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK?

Lapatinib, administered in combination with capecitabine (Xeloda®, Roche), is available via an Expanded Access Programme being conducted under a clinical protocol (EGF103659) for patients who meet the proposed indication i.e. those with advanced or metastatic breast cancer whose tumours overexpress human epidermal growth factor receptor 2 (HER2) and who have received prior therapy including trastuzumab (Herceptin®, Roche).

This programme is expected to be conducted at 30 sites across the UK; there are currently 10 active sites with several more due to open shortly. Further details can be

found on the clinical trial register at:
http://clinicaltrials.gov/ct/show/NCT00338247?order=7

Other clinical trials of lapatinib are ongoing in the UK but not for the indication or with the regimen for which marketing authorisation has been sought.

It is estimated that lapatinib will be made commercially available in the UK during Q3 2007, once marketing authorisation is received.

1.5. Does the technology have regulatory approval outside the UK? If so, please provide details.

Lapatinib, in combination with capecitabine, received FDA approval in the US on 13th March 2007 for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.

Preliminary approval has also been granted in the United Arab Emirates (UAE) and Venezeula.

1.6. Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

GSK expect to submit data on the use of lapatinib as per its licensed indication to the Scottish Medicines Consortium (SMC) in order to allow guidance on the use of the drug in Scotland at the time of marketing authorisation.

1.7. For pharmaceuticals, what formulation (s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Lapatinib ditosylate monohydrate will be available as 250mg film-coated tablets in 70-tablet packs (aluminium foil blisters of 10 tablets per blister strip x 7 strips).

1.8. What is the proposed course of treatment?

For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The recommended dose of lapatinib in combination with capecitabine was established in a phase I study (EGF10005) (De Bono 2003, Schwartz 2004) and is:

Lapatinib 1250mg (5 x 250mg tablets) once daily continuously (at least one hour before, or at least one hour after food).
plus
Capecitabine 2000mg/m^2/ day (as tablets) taken in two doses 12 hours apart on days 1–14 of a 21-day cycle (taken with food or within 30 minutes after food).

Treatment should be continued until disease progression. Median time to progression (TTP) in the pivotal registration study (EGF100151) was 27.1 weeks for patients receiving lapatinib plus capecitabine.

1.9. What is the acquisition cost of the technology (excluding VAT)?

For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The anticipated acquisition cost of lapatinib in the UK is likely to be in the range of £10.45 to £11.60 per tablet (£1589 - £1764 per month).

1.10. What is the setting for the use of this technology?

Lapatinib treatment should only be initiated by a physician experienced in the administration of anti-cancer agents. The SmPCs for other anticancer agents contain similar wording in this respect.

As an oral regimen, lapatinib plus capecitabine may be self-administered by the patient at home (in accordance with appropriate local guidelines).

1.11. For patients being treated with this technology, are there any other aspects that need to be taken into account?

For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Testing for HER2-overexpression is an established part of routine clinical practice in the management of breast cancer and will have taken place prior to trastuzumab treatment, a pre-requisite for the use of lapatinib. There is no requirement for further HER2 testing prior to treatment with lapatinib.

The indication for which marketing authorisation of lapatinib has been sought is in combination with capecitabine. The dosage of capecitabine in combination with lapatinib is 2000mg/m^2/day taken in two divided doses on days 1-14 of a 21-day cycle. This is lower than the dosage recommended on the capecitabine SmPC of 2500mg/m^2/day but was established in a phase I study (EGF10005) as the optimally tolerated regimen (OTR) (De Bono 2003, Schwartz 2004).

Cardiac monitoring was incorporated into the lapatinib clinical trials programme because of the significant and unexpected cardiac toxicity observed with trastuzumab in phase III trials (Seidman 2002; Slamon 2001). However, the available evidence indicates a very low incidence of cardiac events experienced by patients receiving lapatinib (Perez 2006). The proposed SmPC recommends that left ventricular ejection fraction (LVEF) is evaluated prior to initiating lapatinib and during treatment, consistent with the cardiac monitoring undertaken in the trials. The level of monitoring required for lapatinib is likely to be greater than that undertaken for single-agent capecitabine or vinorelbine, but is unlikely to exceed that adopted for trastuzumab in routine clinical practice.

2. Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

The decision problem considered is the clinical and cost-effectiveness of lapatinib plus capecitabine, relative to currently prescribed regimens, in the treatment of HER2-positive advanced or metastatic breast cancer which has progressed following anthracycline, taxane and trastuzumab treatment.

2.1. Intervention

Lapatinib (Tyverb™), in combination with capecitabine (Xeloda®), administered orally until disease progression.

2.2. Population

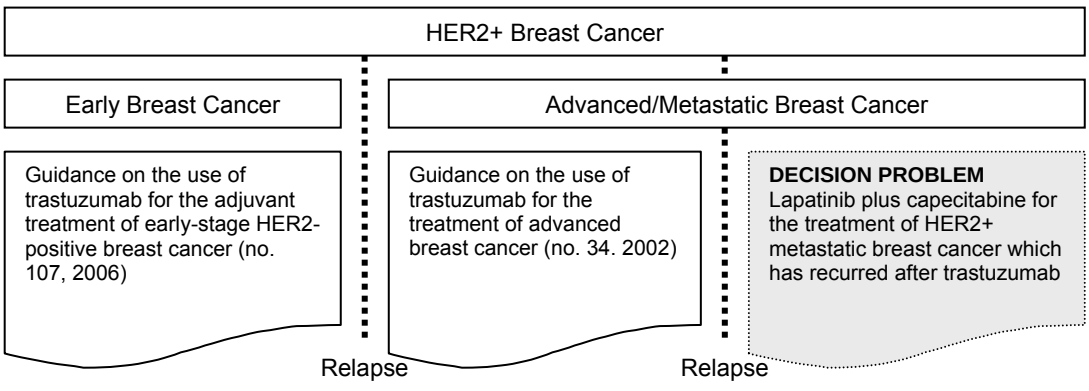
The population under consideration is women with advanced or metastatic breast cancer whose tumours over-express HER2 (ErbB2) and who have received prior therapies, including an anthracycline and a taxane in either the adjuvant or metastatic settings, and trastuzumab for advanced or metastatic disease.

This population reflects the patients selected for EGF100151, the pivotal clinical trial which is the primary evidence base supporting the combination of lapatinib and capecitabine in this setting, and is slightly more restrictive than the likely indication statement which does not stipulate prior use of trastuzumab in the metastatic setting. It is recognised that the population under consideration may reduce in size as the use of trastuzumab in the adjuvant setting increases, and fewer patients progress to receive trastuzumab in the metastatic setting.

Approximately 25-30% of patients with metastatic breast cancer have tumours that overexpress HER2 (Pennault-LLorca 2005). This may be higher than the proportion with HER2-positive (HER2+) disease in a general breast cancer population because of their worse prognosis and increased likelihood of relapse. Note: HER2-overexpressing breast cancer is also known as HER2+ breast cancer and the terms have been used interchangeably in this submission.

Figure 2.1 shows the population under consideration in the context of existing NICE guidance for HER2+ breast cancer.

Figure 2.1. NICE guidance for HER2+ breast cancer



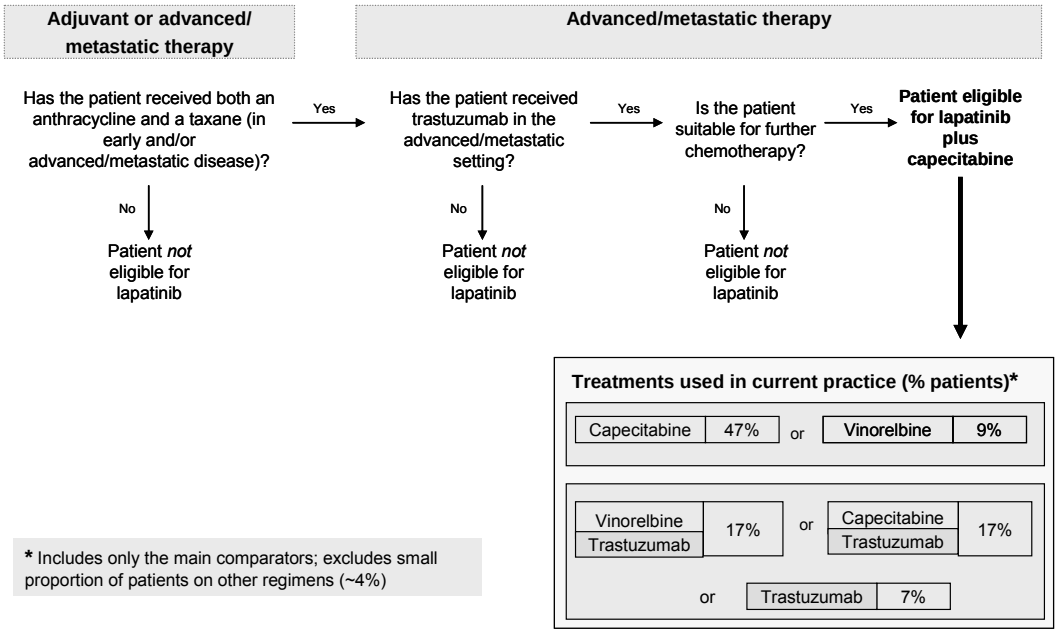
2.3. Comparators

For women whose HER2+ metastatic disease has progressed after trastuzumab there is no tested standard of care and such patients have few treatment options available to them. Continuous suppression of the HER2 receptor is a key factor in improving outcomes for HER2+ patients and there is currently no alternative HER2-targeted therapy for use following trastuzumab, thereby highlighting an area of high unmet need.

The paucity of evidence to support the treatment decision in such patients means that clinicians in routine clinical practice have employed strategies used for non-HER2 overexpressing cancers (such as single-agent chemotherapies which do not target HER2), or have empirically added alternative cytotoxic chemotherapy drugs while continuing trastuzumab. This latter approach is based on limited clinical evidence. The existence of a number of non-randomised studies investigating the continuation of trastuzumab in this way suggests, however, that this is a genuine treatment decision which is understandable in light of the lack of alternative options to suppress HER2. The introduction of lapatinib addresses an unmet need by providing a rational, specific and evidence-based treatment option for this patient population.

To illustrate the position of lapatinib plus capecitabine in relation to other treatments used in clinical practice in the population under consideration a decision pathway for determining eligibility for lapatinib in combination with capecitabine on the basis of previous treatments is shown in Figure 2.2 below. The proportions of patients receiving different regimens are derived from market research (described in more detail in Section 4.1), and confirmed through discussions with clinicians.

Figure 2.2. Decision pathway for determining eligibility for lapatinib treatment on the basis of previous treatments



The comparators in standard use in this population and considered in this submission are therefore:

- Capecitabine monotherapy
- Vinorelbine monotherapy
- Trastuzumab, either in combination with capecitabine or vinorelbine, or as monotherapy

Capecitabine monotherapy

Capecitabine is used in nearly 50% of patients in this population, and it is therefore included as a key comparator in this submission. Capecitabine monotherapy is licensed and recommended by NICE for the treatment of patients with advanced or metastatic breast cancer after failure of both anthracycline- and taxane- containing regimens (Xeloda® SmPC; NICE TA no.62). This guidance does not address the HER2+ population specifically.

Capecitabine cannot be considered a comparator in isolation, as this would exclude a significant proportion of the relevant patient population who receive other interventions in routine clinical practice in the UK.

Trastuzumab

In the absence of other licensed HER2-targeted alternatives, approximately 40-45% of patients who develop progressive disease while being treated with trastuzumab in the metastatic setting continue to receive trastuzumab beyond disease progression, either alone, or more commonly in combination with cytotoxic chemotherapy, in some cases through multiple lines of therapy. Trastuzumab beyond disease progression – either alone, or combination with capecitabine or vinorelbine - is considered as a comparator in this submission on the basis of its wide usage within UK clinical practice..

Vinorelbine monotherapy

Vinorelbine is used in patients who have developed progressive disease on trastuzumab-containing regimens, either alone or in combination with trastuzumab. Vinorelbine is licensed for the treatment of advanced breast cancer relapsing after or refractory to an anthracycline (Navelbine® SmPC) and is recommended by NICE as one option for the second-line or later treatment of advanced breast cancer when anthracyline-based regimens have failed or are unsuitable (NICE TA no. 54). Again, the HER2+ population is not specifically addressed by this guidance.

Other therapies

A number of other agents may be used infrequently in this setting, and due to their limited and inconsistent use they are not considered valid comparators in this appraisal of lapatinib. Taxane rechallenge is rare in patients who have already received an anthracycline, taxane and trastuzumab. Similarly gemcitabine is not commonly used in this post-first-line population. Other therapies such as taxanes and gemcitabine are therefore not suitable for inclusion as comparators in this appraisal.

2.4. Outcomes

The efficacy and safety of lapatinib in combination with capecitabine compared with capecitabine alone has been established in a phase III registration trial (EGF100151) (Geyer 2006b).

Outcome measures included:

<u>Primary endpoint</u>

- Time to progression (TTP) – by independent review

TTP is an appropriate and sensitive parameter for assessing treatment benefit in patients with advanced/metastatic disease. It is considered by clinical oncologists and regulators to be a valid endpoint in this setting.

Secondary endpoints

- Progression-free survival (PFS)
- Response rates (overall response rate (ORR), clinical benefit rate (CBR))
- Overall survival (OS)
- Health-related quality of life (HRQoL)
- Adverse effects possibly related to study treatment.

The incidence of brain metastases as the site of first relapse in both treatment arms was examined as a post-hoc analysis.

The clinical and economic case for lapatinib in combination with capecitabine in this submission is based on the independently-assessed clinical endpoints as is usual in such situations.

2.5. Economic analysis

A systematic review of the literature found no existing economic evaluations of lapatinib in breast cancer so a de novo modelled cost-utility analysis was undertaken. The health economic model uses survival modelling methodology to estimate the expected time to disease progression and death for women with trastuzumab-pre-treated HER2-overexpressing advanced or metastatic breast cancer, treated with lapatinib plus capecitabine and each of the five comparator regimens.

All outcomes and costs are evaluated over a 5-year time horizon beginning with the start of treatment. This time horizon approximates a lifetime projection for women with HER2+ advanced or metastatic breast cancer who have received prior treatment with trastuzumab. The time to progression and death differs according to treatment strategy, and is dependent on time-to-event data sourced from the pivotal EGF100151 trial, and from non-randomised studies of trastuzumab. Costs are considered from a NHS perspective.

The key outcomes in the economic analysis are:

- Progression-free life years (PFLYs)
- Quality-adjusted life years (QALYs)
- Administration costs
- Monitoring costs
- Incremental cost per progression-free life year gained
- Incremental cost per quality-adjusted life year gained

2.6. Special considerations and other issues

The following issues should be considered in relation to this submission:

Patients

Patients with HER2+ advanced or metastatic breast cancer who progress on or following treatment with trastuzumab, anthracyclines and taxanes represent a population for whom there are no specifically licensed or proven options, and no standard of care. In the absence of options proven specifically for use in HER2+ disease that has progressed following the above treatments, alternative treatment strategies have evolved and are used in clinical practice in the UK.

Patients can be broadly categorised into two groups, according to the treatment strategy adopted:

(i) Over half of patients who continue on treatment in these circumstances receive a non-HER2-targeted cytotoxic chemotherapy agent, e.g. capecitabine or vinorelbine;

(ii) In the absence of an alternative HER2-suppressing agent, 40-45% of patients continue to receive trastuzumab beyond disease progression, either alone, or in combination with cytotoxic chemotherapy. Literature, market research and clinical opinion indicate that those patients who are most likely to receive trastuzumab beyond progression are those in whom the drug still appears to be having some effect, despite progression (for example those patients with stable disease at most sites with progression at an isolated site, including those with brain metastases (Montemurro 2006, Dendrite data – Appendix 9.4, Kirsch 2005), those with few metastases in the soft tissues or bone (Garcia-Saenz 2005)) and those with a good response to an initial trastuzumab regimen (Montemurro 2006).

Study EGF100151 inclusion criteria selected a broad group of patients whose disease had progressed following trastuzumab therapy, and did not specify or stratify for those patients described above for whom trastuzumab continued beyond progression appears to be having some effect. However, it is likely that the study population recruited was inclusive of this group, and is therefore broadly representative of such patients.

Survival data

Study EGF100151 was designed to detect a statistically significant difference in overall survival between treatment groups, as a secondary endpoint. However, enrolment was halted early on the unanimous recommendation of the Independent Data Monitoring Committee (IDMC), because a pre-planned interim analysis yielded a statistically significant result in the primary endpoint (TTP), and the trial had exceeded the predetermined stopping criteria outlined in the committee charter. It is therefore unlikely that there will be sufficient power to confirm a significant difference in overall survival once the data are mature. Women receiving capecitabine alone were offered the option of switching to lapatinib plus capecitabine, which was taken up by 33 out of the 39 patients who were still receiving capecitabine therapy, further confounding the opportunity to demonstrate a significant difference in overall survival. Modelling and extrapolation of the overall survival estimates has therefore been necessary.

It should be noted that the lack of significant overall survival data is a common issue in this disease area, where for ethical reasons it is necessary to terminate studies once the primary endpoint has been met.

Availability of evidence

There is limited robust clinical evidence reported in this population. Indeed, a systematic review of the literature to identify evidence in patients who would be eligible for lapatinib treatment by virtue of their HER2 status and treatment history has identified only one randomised controlled trial which met these requirements. This is the pivotal registration trial comparing lapatinib plus capecitabine with capecitabine alone (EGF100151; Geyer 2006b) that forms the focus of this submission. As a consequence of these limited data, the relative effectiveness of lapatinib (plus capecitabine) versus therapies other than capecitabine has been difficult to determine with certainty.

Due to limitations in the evidence base supporting treatments in this setting it has been necessary to perform indirect comparisons using non-randomised, non-comparative data sources such as single-arm studies and observational data.

Brain metastases and HER2+ breast cancer

Brain metastases are an increasing clinical problem in patients with HER2+ breast cancer (Lin 2004), for which there are currently limited treatment options. Historically, approximately 6-16% of women with metastatic breast cancer developed clinically apparent brain metastases (Lin 2004). However, between 28 and 43% of patients receiving trastuzmab in the metastatic setting have been reported to relapse with brain metastases (Bendell 2003; Lin 2004). This apparent increase may reflect the biology of HER2+ tumours and the inability of trastuzumab, a monoclonal antibody, to pass through the blood-brain barrier (Burstein 2005; Lin 2007; Stemmler 2006). Hence, while trastuzumab effectively controls non-central nervous system (CNS) disease, the CNS becomes a 'sanctuary site' (Clayton 2004; Lin 2007). As a small molecule, lapatinib should be able to cross the blood-brain-barrier and preliminary data suggest that it may have some activity against brain metastases (Geyer 2006b; Lin 2006; Van den Abbeele 2006).

Additional benefits of lapatinib

The recommendations of the recently published White Paper: Our Health, Our Care, Our Say: A New Direction for Community Services 2006 (DoH 2006), note that more care for cancer patients should be provided outside the hospital setting, including in the home where appropriate. Lapatinib plus capecitabine clearly meets this directive, offering patients the convenience of an oral treatment which may be self-administered at home, reducing time spent in hospital and the expense and inconvenience of hospital attendance, when compared with intravenous therapies. As an orally-administered regimen, lapatinib plus capecitabine might therefore help to reduce pressure on hospital administered intravenous chemotherapy service capacity.

Lapatinib has a unique mode of action and was specifically designed to selectively target both the Epidermal Growth Factor Receptor (EGFR, ErbB1) and HER2 (ErbB2) receptors (Johnston S 2006), which are frequently overexpressed in breast cancer and are associated with cancer cell proliferation and tumour growth.

3. Executive summary

3.1. Background

Breast cancer is the most common malignancy among women in the UK, accounting for about 30% of all cancers in women and 17% of all female cancer deaths.

Metastatic breast cancer is, in almost all cases, incurable. The goals of treatment are to prolong survival and time to disease progression, and to maximise quality of life with an acceptable toxicity profile.

Approximately 25-30% of patients with metastatic breast cancer have tumours that over-express HER2. HER2-positive (HER2+) tumours tend to be more aggressive with a more rapid disease progression and reduced survival time. Around one third of patients with HER2+ metastatic breast cancer will develop metastases in the brain, a condition associated with substantial morbidity, mortality and impairment of quality of life.

Suppression of the HER2-receptor is recognised as key to improving outcomes in patients with HER2+ disease. Trastuzumab (Herceptin®), the only licensed HER2-targeted therapy currently available in the UK, has shown significant activity in HER2+ breast cancer both alone and in combination with cytotoxic chemotherapy.

For patients with HER2+ metastatic breast cancer, first-line treatment typically consists of trastuzumab in combination with a taxane, but following further progression there are few treatment options available to patients, and there is no alternative HER2-targeted therapy.

3.2. Lapatinib

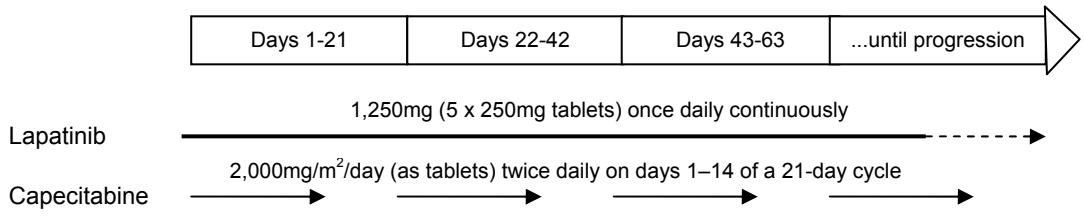
Lapatinib ditosylate monohydrate (Tyverb™) is an orally-administered treatment, available as 250mg film-coated tablets, in 70-tablet packs (aluminium foil blisters of 10 tablets per blister strip x 7 strips).

Lapatinib has a unique mode of action, selectively targeting both the EGFR (ErbB1) and HER2 (ErbB2) receptors. There is evidence to suggest that as a small molecule lapatinib is able to cross the blood-brain-barrier and penetrate the CNS, unlike monoclonal antibodies, such as trastuzumab.

Lapatinib is likely to be indicated for use in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumours over-express HER2 (ErbB2) and who have received prior therapy including trastuzumab, an anthracycline and a taxane. Restrictions to lapatinib are: i) initiated only by a physician experienced in the administration of anti-cancer agents; ii) baseline left ventricular ejection fraction (LVEF) within the institutional limits of normal.

Lapatinib will be indicated in combination with capecitabine according to the following regimen:

Figure 3.1. Treatment regimen for lapatinib plus capecitabine



Treatment should be continued until disease progression.

The acquisition cost of lapatinib in the UK is likely to be in the range of £10.45 to £11.60 per tablet (£1589 - £1764 per month).

A marketing authorisation application (MAA) was filed with the European Medicines Evaluation Agency (EMEA) on 4th October 2006 and is now under review via the Centralised procedure. It is estimated that marketing authorisation will be received in 3Q 2007.

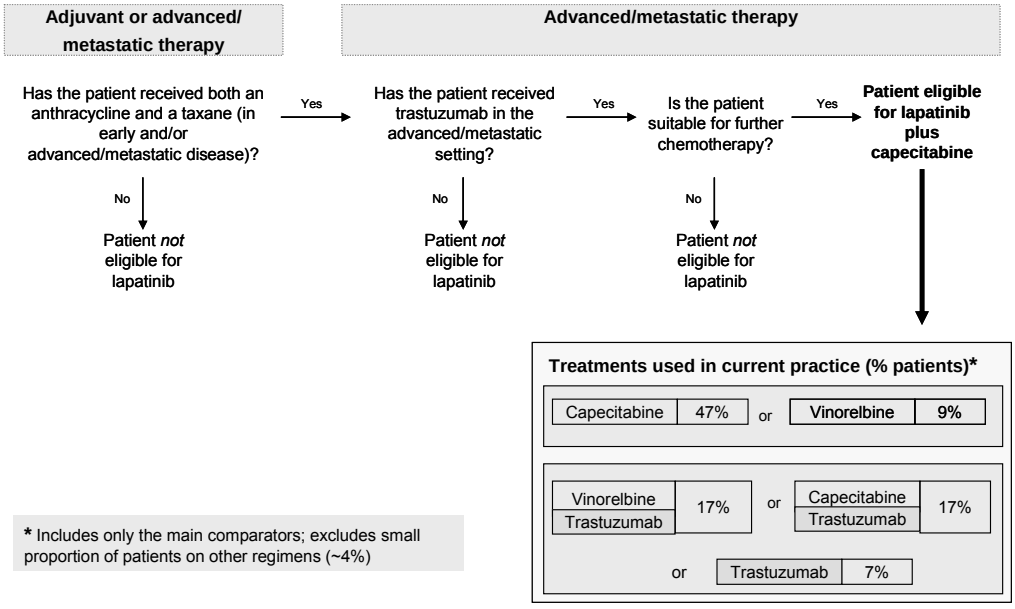
3.3. Population

The population selected in the pivotal randomised controlled trial (RCT) on which this submission is based (EGF100151) is women with HER2+ advanced or metastatic breast cancer, who require therapy beyond first-line and have received prior therapies that include an anthracycline and a taxane in either the adjuvant or metastatic settings, and trastuzumab for advanced or metastatic disease.

3.4. Comparators

Discussions with UK breast oncologists and subsequent market research studies undertaken to identify and quantify the extent of use of different regimens in the population under consideration suggest that in current practice various treatment strategies have evolved to treat HER2+ disease following progression on trastuzumab in the metastatic setting and prior treatment with an anthracycline and a taxane (see Section 4.1 for more details; Figure 3.2 below).

Figure 3.2. Decision pathway for determining eligibility for lapatinib treatment on the basis of previous treatments



Patients can be categorised broadly into two groups, according to the strategy adopted:

i) Over 50% of patients who continue on treatment following progression on trastuzumab receive a cytotoxic chemotherapy agent, e.g. capecitabine or vinorelbine. These drugs are not licensed specifically for use in HER2+ disease, and existing NICE guidance on their use does not specifically address this group of patients thus demonstrating the continued unmet need.

ii) Acknowledging the importance of continued HER2 suppression in HER2+ patients, clinicians continue to prescribe trastuzumab beyond disease progression in approximately 40-45% of patients, either alone, or more commonly in combination with cytotoxic chemotherapy.

Figure 3.2 outlines the treatments used in current clinical practice in the eligible population, and therefore defines the comparators in the decision problem (capecitabine, trastuzumab with or without cytotoxic chemotherapy, or vinorelbine).

Patients who are most likely to receive trastuzumab beyond progression are those in whom the drug still appears to be having some effect, despite progression (for example those patients with stable disease at most sites with progression at an isolated site, including those with brain metastases, those with few metastases in the soft tissues or bone, and those with a good response to an initial trastuzumab regimen).

3.5. Comparative clinical effectiveness

A systematic review was undertaken to identify clinical evidence for lapatinib and its comparators in the target population. This review identified only one directly relevant study for lapatinib - pivotal registration trial EGF100151 - which compared lapatinib plus capecitabine with capecitabine alone, administered as per the indicated regimen. This study forms the basis of the evaluation of the effectiveness of lapatinib and capecitabine in this submission.

3.5.1. Lapatinib plus capecitabine versus capecitabine

Study EGF100151 included a total of 399 patients (198 in the lapatinib plus capecitabine arm, and 201 in the capecitabine only arm). Enrolment was halted early on the recommendation of the Independent Data Monitoring Committee due to a statistically significant and clinically meaningful improvement in time-to-progression (TTP), the primary endpoint, which met pre-defined stopping criteria. Although the study was originally powered to detect a statistically significant difference in overall survival (OS), the early termination of the trial means that a statistically significant difference is now unlikely to be demonstrated.

The results presented below are from the latest, unpublished analysis of EGF100151 (3 April 2006 cut-off; anticipated publication in June 2007), and therefore they differ slightly from the published results (November 2005 cut-off) [Geyer 2006b].

Lapatinib plus capecitabine significantly increased the independently-assessed median TTP (the primary endpoint) compared with capecitabine alone (27.1 vs. 18.6 weeks, hazard ratio (HR) = 0.57 (95% confidence interval (CI) 0.43, 0.77; p=0.00013). Statistically significant differences favouring lapatinib plus capecitabine were observed for the secondary endpoints, progression-free survival, response rate and clinical benefit response by an independent review (p=0.000033, p=0.017 and p=0.008 respectively). There was no detriment to health-related quality of life in patients receiving lapatinib plus capecitabine.

At the time of the data cut-off, there was a 22% reduction in risk of death for subjects receiving lapatinib plus capecitabine relative to capecitabine alone (median OS 67.7 weeks versus 66.6 weeks respectively; HR: 0.78; 95% CI: 0.55, 1.12, log-rank 2 sided p=0.177).

Lapatinib plus capecitabine was associated with a significantly lower incidence of brain metastases as the first site of relapse compared with capecitabine alone (4 versus 13 cases respectively; p=0.0445), suggesting that lapatinib may have some preventative activity against brain metastases.

Lapatinib plus capecitabine appears to be well tolerated with a manageable toxicity profile. The addition of lapatinib to capecitabine does not greatly alter the tolerability profile compared with capecitabine alone. Adverse events observed with lapatinib were generally mild to moderate, and transient in nature. This is further demonstrated by the maintenance of quality of life for patients in EGF100151. The overall cardiac

safety experience for lapatinib to date shows very few cases [*n=70/4695; 1.5%*] of decreased LVEF, which were largely asymptomatic [1.3%] and reversible.

The characteristics of patients in the EGF100151 study were closely representative of those patients with metastatic breast cancer who have received trastuzumab, an anthracycline and a taxane in UK clinical practice. Indeed the study included 43 UK patients. Hence, there are no obvious reasons why the results achieved with lapatinib plus capecitabine in the study should not translate into routine clinical practice in England and Wales.

3.5.2. Lapatinib plus capecitabine versus vinorelbine

The systematic review did not identify any clinical evidence for vinorelbine monotherapy in this post-trastuzumab metastatic setting. Furthermore an attempt to find comparative studies of vinorelbine versus capecitabine in metastatic breast cancer, without the requirement for pre-treatment with taxane, anthracycline and trastuzumab, in order to extrapolate and perform indirect analyses, yielded no results. In order to make a comparison between lapatinib plus capecitabine and vinorelbine we made the assumption that vinorelbine's effectiveness is likely to be similar to capecitabine's, as suggested in the NICE review of capecitabine (TA no. 62). [redacted]

3.5.3. Lapatinib plus capecitabine versus trastuzumab regimens

There were no comparative studies identified in this setting that allow formal direct or indirect comparison between lapatinib/capecitabine and trastuzumab-containing regimens. The review identified 12 studies examining the continuation of trastuzumab following progression on trastuzumab-based regimens; these were non-randomised, predominantly observational, prospective and retrospective studies. The existence and number of these studies suggests that the continuation of trastuzumab after patients have progressed on it is a real and important treatment decision, worthy of evaluation. It is not possible from these studies to differentiate between the efficacy of trastuzumab when given alone, or when given in combination with other chemotherapy agents.

To provide a comparison of the clinical effectiveness of trastuzumab regimens versus lapatinib plus capecitabine the progression data from these studies was pooled, with a weighting applied to account for sample size. This yielded an estimate of median TTP for trastuzumab of 21.8 weeks (95% CI 19.5, 24.3), which lies between the median TTPs for capecitabine and for lapatinib plus capecitabine.

3.6. Cost-effectiveness of lapatinib

3.6.1. Approach to the economic evaluation

A systematic review of the literature found no existing economic evaluations of lapatinib in breast cancer so a de novo cost-utility analysis was undertaken using a survival modelling approach within a decision-analytic framework. The modelling methodology is analogous to the state transition (Markov) approach, estimating costs and health outcomes based upon time spent in three discrete states of health: alive prior to disease progression, alive following disease progression and dead. The proportions of patients expected to reside in each of the states are based on estimated survival functions for progression-free survival and overall survival.

For lapatinib plus capecitabine and capecitabine and vinorelbine monotherapies, survival data were modelled directly from EGF100151 patient-level data (April 2006

cut-off). The efficacy of trastuzumab-based comparators was modelled via pooled TTP data obtained from the systematic review.

3.6.2. Pivotal assumptions:

The pivotal assumptions in the economic analysis are listed below:

- Proportional hazards assumption for estimating the event hazard rate, for progression of disease or death, in patients receiving lapatinib plus capecitabine from the capecitabine-only results.
- Vinorelbine efficacy is similar to that of capecitabine.
- The efficacy of all trastuzumab regimens is similar when continued after initial progression on trastuzumab.
- The EGF100151 study population is broadly representative of patients who go on to receive either single agent chemotherapy, or continued trastuzumab regimens, and they are therefore likely to experience similar benefits from lapatinib plus capecitabine.
- The progression-free survival benefit associated with trastuzumab-containing regimens is proportional to the progression-free survival benefit of lapatinib plus capecitabine. Following disease progression, the duration of post-progression survival on trastuzumab-containing regimens is equivalent to that of lapatinib plus capecitabine.
- Health-related quality of life is influenced primarily by the presence or absence of disease progression.
- Impact of adverse events on a patient's level of health-related quality of life is independent of the treatment regimen received.
- Acquisition cost of lapatinib is £11.00 per tablet (mid-range).
- Most non-drug costs are independent of treatment (with the exception of higher hospital administration and wastage costs for intravenous (IV) therapies) and instead depend on whether disease progression has occurred.
- Relative dose intensity is assumed to be lower than 100% for all drugs based on estimates for combination therapy and monotherapy within study EGF100151.

3.6.3. Cost-effectiveness results

3.6.3.1. Lapatinib plus capecitabine versus capecitabine or vinorelbine

In patients for whom the current treatment strategy would normally be to prescribe a single agent chemotherapy following progression after trastuzumab in the metastatic setting, the base case incremental cost per quality adjusted life year (QALY) for lapatinib plus capecitabine is £81,251 versus capecitabine, and £67,847 versus vinorelbine. Probabilistic sensitivity analyses suggest that the likelihood of lapatinib plus capecitabine having an incremental cost-utility ratio lower than £20,000/QALY is 1% in this scenario (5-7% for a threshold of £30,000/QALY).

3.6.3.2. Lapatinib plus capecitabine versus trastuzumab regimens

In patients for whom the current treatment strategy would be to continue on a trastuzumab-containing regimen in the context of maintaining HER2 suppression, lapatinib plus capecitabine dominates continued trastuzumab regimens in the base case analysis (i.e. lapatinib plus capecitabine is both more effective and less costly than estimates for trastuzumab regimens). Probabilistic sensitivity analyses suggest that in this scenario the likelihood that lapatinib plus capecitabine has an incremental cost-utility ratio lower than £20,000/QALY ranges from 85-95% in the three comparisons (83-95% for the £30,000 threshold).

3.6.3.3. Uncertainty

A key area of uncertainty in this evaluation stems from the immature and incomplete nature of the survival data from EGF100151, and the consequent need to model survival. The extrapolation used a Weibull distribution to fit the survival curves. A proportional hazards approach was used to estimate the survival function for lapatinib plus capecitabine, in relation to capecitabine. These approaches are explored within section 6 of the submission.

Deterministic sensitivity analyses show that the incremental cost-effectiveness of lapatinib plus capecitabine is stable to changes in most of the model parameters However, there are several key drivers in the lapatinib plus capecitabine versus capecitabine or vinorelbine alone comparisons, in particular the proportional hazards assumption.

Key sensitivities in the trastuzumab-based comparisons relate to how the medications are given (wastage, number of chemotherapy cycles, and frequency of trastuzumab and vinorelbine administration). In a wide-ranging sensitivity analysis, the incremental cost-effectiveness ratios (ICERs) for lapatinib plus capecitabine versus trastuzumab-containing regimens remained below £20,000/QALY in all except 2 of the 18 scenarios tested; however, the ICERs still remained below £30,000/QALY).

The necessary reliance on indirect comparisons using non-randomised data sources in the comparison with trastuzumab regimens was tested in sensitivity analysis using broad assumptions for trastuzumab effectiveness (ranging from effectiveness equivalence with capecitabine alone, to equivalence with lapatinib plus capecitabine), and this did not alter the dominance seen in the base case.

The factors above do not change the results in relation to the decision problem: Lapatinib plus capecitabine consistently remains a cost-effective treatment option in patients who would otherwise continue to receive trastuzumab beyond progression.

3.7. Impact on the NHS

The total incremental cost of replacing current treatments with lapatinib plus capecitabine in all patients who are eligible to receive it is estimated at approximately £1,285,000 in the first year, rising to £6,427,000 at five years (assuming a rate of uptake of 10 percentage points per annum, and uniform replacement of the different regimens).

The adoption of lapatinib plus capecitabine as an alternative and evidence-based treatment option for patients who would otherwise have received continued trastuzumab would result in cost savings of £190,000 to £951,000 over five years, assuming the same 10 percentage point uptake year-on-year.

The introduction of lapatinib plus capecitabine, as an oral combination regimen, has the potential to reduce the need for IV administration of chemotherapy and/or trastuzumab in the hospital setting, thereby releasing capacity for deployment elsewhere in chemotherapy services. Additionally the oral regimen offers potential benefits to patients in terms of convenience and preference, at a stage in their disease where their time and energy is limited.

3.8. Conclusions

Lapatinib plus capecitabine provides a new, evidence-based and innovative option for continued HER2-targeted suppression in patients with advanced or metastatic breast cancer who have progressed on trastuzumab, for whom there are no proven or specifically licensed treatment options.

Lapatinib added to capecitabine extends time to disease progression and may extend overall survival, without impairing quality of life and with an acceptable toxicity profile.

Lapatinib plus capecitabine provides superior outcomes in terms of progression-free life years, life years and QALYs versus single agent chemotherapies. For patients who would currently be continued on a trastuzumab regimen beyond progression lapatinib plus capecitabine is a clinical and cost-effective alternative. Examples of patients who may be suitable for continued trastuzumab include: those with stable disease at most sites with progression at an isolated site, few metastases in the soft tissues or bone and previous good response to trastuzumab. These patients represent a group for whom lapatinib plus capecitabine should be recommended as a cost-effective use of NHS resources.

Lapatinib plus capecitabine has the added benefits of oral administration, and the potential to be active against brain metastases.

4. Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1. Overview of breast cancer and current treatments

Provide a brief overview of the disease/condition for which the technology is to be used. Provide details of the treatment pathway and current treatment options at each stage.

Disease epidemiology

Breast cancer is by far the most common malignancy among women in the UK, with 38,909 cases reported in England and Wales in 2003 (Cancer Research UK incidence statistics), accounting for about 30% of all cancers in women. While incidence rates continue to rise, breast cancer mortality rates have fallen in the UK since 1989. Nevertheless, breast cancer resulted in 10,945 deaths in England and Wales in 2005. It accounts for 17% of female deaths from cancer in the UK and is the most common cause of death in women aged 35-54 years (Cancer Research UK mortality statistics).

Prognosis

A patient's prognosis is affected by the stage/extent of the disease at the time of diagnosis and its characteristics, including hormone- and HER2- receptor status (Lohrisch 2001; Nicolini 2006). Once breast cancer has spread to the areas surrounding the breast (Stage IIIA & IIIB: locally advanced disease) or to organs remote from the breast (Stage IV: metastatic disease), it is, in almost all cases, incurable. Between 10 and 15% of patients present with locally advanced or metastatic disease at first diagnosis (Lewis 2002). In addition, around 40-50% of patients diagnosed with early-stage breast cancer who receive treatment with curative-intent will develop metastatic disease (NICE TA no.34; Polychronis 2005). Common sites of metastasis include bone, lung, liver, and brain (American Cancer Society).

Approximately 25-30% of metastatic breast cancer patients have tumours that over-express HER2 (Penault-Lorca 2005; Appendix 9.4), known as HER2-positive (HER2+) breast cancer. HER2-overexpression is associated with aggressive tumour behaviour, decreased responsiveness to both chemotherapy and hormonal therapy, and a more rapid disease progression (Holbro 2003; Slamon 1987). The average survival time, with treatment, after diagnosis of advanced or metastatic breast cancer is 18-24 months; this is reduced by up to 50% in patients with HER2+ disease (NICE TA no. 34).

HER2-positivity has been recognised as a significant risk factor for the development of brain metastases (Altaha 2004; Gabos 2006; Souglakos 2006), a condition associated with substantial morbidity and mortality (Lin 2004; Lin 2007). Around one third of patients with HER2+ metastatic breast cancer treated with trastuzumab have been reported to develop metastases in the brain (Bendell 2003; Lin 2004; Lin 2007). Breast cancer patients with brain metastases incur significantly more healthcare resources compared to those without brain metastases (GSK data on file).

Treatment pathway/current options in advanced or metastatic breast cancer

The goals of treating advanced or metastatic breast cancer are to prolong survival and time to disease progression and to relieve symptoms with an acceptable toxicity profile, thereby maintaining a reasonable quality of life. The main classes of anti-

cancer agents currently used in the medical management of advanced or metastatic breast cancer are: endocrine therapy, cytotoxic chemotherapy and HER2-targeted therapy. Choice of treatment is influenced by many factors relating to both the patient and tumour characteristics. These include the patient's age, performance status, menopausal status, previous treatment, extent and location of metastases, and oestrogen-, progesterone- and HER2-receptor status.

Suppression of the HER2-receptor is recognised as a key objective in improving outcomes in patients with HER2+ breast cancer. Trastuzumab, a monoclonal antibody, targeted at the HER2-receptor, has been shown to have significant activity in the first-line HER2+ metastatic setting both as a single agent and in combination with cytotoxic chemotherapy (Marty 2005; Slamon 2001; Vogel 2002). As the only HER2-targeted agent with marketing authorisation in the UK, trastuzumab-based regimens have become the standard of care in the HER2+ population. However, the majority of patients receiving trastuzumab for metastatic disease will progress within 12 months of starting treatment (Slamon 2001; Vogel 2002).

Strategies used following progression on trastuzumab

For women with HER2+ metastatic disease who progress after trastuzumab there is no tested standard of care and few treatment options available. There is currently no alternative licensed HER2-suppressing agent, thereby highlighting an area of high unmet need.

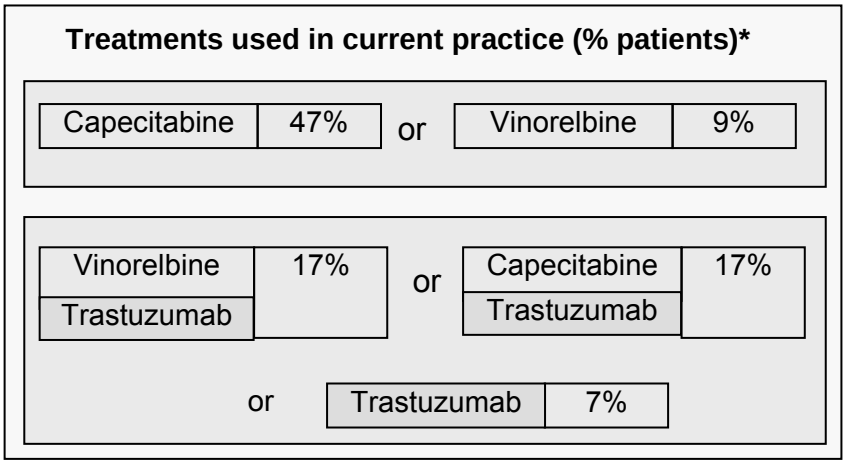
To establish the treatment pathway in UK clinical practice, GlaxoSmithKline held discussions with a number of UK breast oncologists as part of advisory boards or as individual conversations. This confirmed that the most common approach in this population is single-agent chemotherapy, usually capecitabine or in some cases vinorelbine. However, it is also clear that many UK clinicians continue to give trastuzumab beyond disease progression in the metastatic setting. This is either as monotherapy or by combining trastuzumab with chemotherapy, most frequently with capecitabine or vinorelbine.

Three market research studies were conducted with UK oncologists to try and establish the extent and rationale for this use (no. of oncologists = 41, 50, 90). These all confirmed that use of trastuzumab beyond progression is common in the metastatic setting. The studies indicate that whilst practice varies between clinicians, on average they continue trastuzumab (beyond progression in the first-line metastatic setting) in 39%, 29%, and 41% of their patients respectively. The same studies suggest that trastuzumab monotherapy accounts for 6-12% of all therapies used in this setting (see Appendix 9.4.2. for further details).

Determining the relative extent of current use of each of the therapies is problematic with the data sources available. This is because it is difficult to identify the specific patient population without information on each line of treatment and relative instances of progression. The most appropriate data source available is the Intercontinental Marketing Services (IMS) Oncology Analyzer because it is possible to determine prior therapies for patients and identify probable instances of progression. The percentages in Figure 4.1 are derived from the IMS Oncology Analyzer (see Appendix 9.4.1. for further details). The number of patients in the IMS Oncology Analyzer sample that had progressed on trastuzumab after previous treatment with a taxane and an anthracycline (i.e. relevant to the setting for lapatinib) is small (n=24). However, this source is the largest, most comprehensive, commercially available oncology patient-record database. In addition, whilst acknowledging that local variations occur, the relative percentages in Figure 4.1 appear to be reasonably representative of clinical practice across the UK as they agree well with the market research and clinician feedback described above.

Feedback from UK oncologists and the IMS Oncology Analyzer market research also indicate that taxane re-challenge is infrequent in this setting as patients have already received a taxane at an earlier stage.

Figure 4.1: Treatments used in current UK clinical practice in patients with HER2+ metastatic breast cancer following progression on trastuzumab



*excludes small proportion of patients on other regimens

To summarise, the treatment strategies used in this patient population fall into two broad groups:

iii) Over 50% of patients who continue on treatment in these circumstances receive a cytotoxic chemotherapy agent (e.g. capecitabine or vinorelbine), in the absence of an alternative HER2-targeted therapy. These drugs are not licensed specifically for use in HER2+ disease, and existing NICE guidance on their use does not specifically address the HER2+ population.

iv) Acknowledging the importance of continued HER2 suppression in HER2+ patients, clinicians continue to prescribe trastuzumab beyond disease progression in approximately 40-45% of patients, either alone, or more commonly in combination with cytotoxic chemotherapy.

Literature, market research and clinical opinion indicate that those patients who are most likely to receive trastuzumab beyond progression are those in whom the drug still appears to be having some effect, despite progression (for example those patients with stable disease at most sites with progression at an isolated site, including those with brain metastases (Montemurro 2006, Dendrite data – Appendix 9.4, Kirsch 2005), those with few metastases in the soft tissues or bone (Garcia-Saenz 2005)) and those with a good response to an initial trastuzumab regimen (Montemurro 2006).

4.2. What was the rationale for the development of the new technology?

Activation of the HER2-receptor is recognised as a key driver of cancer cell proliferation and tumour progression. Thus, blocking HER2-mediated signalling pathways is an integral part of therapy for HER2-overexpressing breast cancer. The clinical benefit of this approach has been demonstrated with trastuzumab, the first and only licensed anti-HER2 therapy. However, the majority of metastatic patients who initially respond to trastuzumab progress within a year of initiating treatment (Nahta 2006).

Patients with HER2+ advanced or metastatic breast cancer who progress after trastuzumab have few therapeutic options available to them and therefore represent a population with a high unmet clinical need. Given that HER2 suppression is a

crucial component of treatment for patients with HER2+ disease, there is a clear need for alternative HER2-targeted therapies.

Lapatinib, a small molecule dual tyrosine kinase inhibitor (TKI) was specifically designed to selectively target both the epidermal growth factor receptor 1 (EGFR, ErbB1) and HER2 (ErbB2) receptors (Johnston S 2006; Moy 2006). A compound that inhibits both EGFR and HER2 may have therapeutic advantages over agents that inhibit only one of these receptors, as well as being useful in tumours that overexpress either one or both receptors (Johnston S 2006). Other factors that led to the development of lapatinib were that small molecule TKIs should inhibit the activity of HER2 receptors with truncated extracellular domains (by binding intracellularly) and they also have the potential to cross the blood-brain-barrier (unlike large monoclonal antibodies) (see Section 4.3).

Capecitabine (a 5-fluorouracil (5-FU) oral prodrug) is an appropriate agent for combination with lapatinib in this setting. Capecitabine is licensed and recommended by NICE after the failure of anthracyclines and taxanes (Xeloda SmPC; NICE TA no.62). *In vitro* data indicate that the combination of capecitabine with ErbB inhibitors can have synergistic activity (Budman 2002; Budman 2006; Magne 2003).

Lapatinib, in combination with capecitabine, therefore provides a rational and specific option for continued HER2-suppression in patients who have progressed on a trastuzumab-based regimen. In addition, the combination is an orally-administered regimen which may have additional benefits such as self-administration by the patient at home and the potential to reduce pressure on hospital-administered intravenous chemotherapy service capacity.

4.3. What is the principal mechanism of action of the new technology?

Lapatinib is a potent inhibitor of the kinase component of two members of the human epidermal growth factor receptor (HER) family – EGFR (ErbB1) and HER2 (ErbB2) (Johnston S 2006; Moy 2006; Nelson 2006). It belongs to the 4-anilinoquinazoline class of tyrosine kinase inhibitors which compete intracellularly with ATP for its receptor binding site (Shewchuk 2000) to inhibit the cell proliferation and survival pathways (Rusnak 2001; Xia 2002). It has a unique mode of action in being the only small molecule, dual kinase inhibitor (SMDKI).

As a dual kinase inhibitor, lapatinib can block signalling through homodimers composed of either EGFR or HER2 or through heterodimers of EGFR or HER2 with other HER family members. Thus, lapatinib has the potential to inhibit multiple signalling pathways simultaneously and may provide more complete blockade of HER signal transduction than agents that target single receptors (Johnston S 2006).

Monoclonal antibodies, like trastuzumab, bind to the extracellular domain of the HER2 receptor. By binding intracellularly, lapatinib has been shown to have activity against receptors that have a truncated or mutated extracellular domain whereas trastuzumab neither binds nor inhibits such receptors (Moy 2006; Xia 2004), a possible mechanism for trastuzumab resistance (Nahta 2006). Evidence suggests that lapatinib is able to cross the blood-brain-barrier and penetrate the CNS (EGF100151; Lin 2006; Van den Abbeele 2006).

4.4. What is the suggested place for this technology with respect to treatments currently available for managing the disease/ condition?

The likely indication for lapatinib is in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress

HER2 (ErbB2) and who have received prior therapy including trastuzumab, an anthracycline and a taxane.

Lapatinib plus capecitabine therefore provides a new and innovative option for a further line of treatment involving continued HER2 suppression in patients with HER2+ advanced or metastatic breast cancer whose disease has progressed on a trastuzumab-based regimen, meeting a previously unmet need.

4.5. Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice?

Patients with HER2+ advanced or metastatic breast cancer who progress on or following treatment with trastuzumab represent a population for whom there are no specifically licensed or tested treatment options.

The paucity of evidence to support the treatment decision in such patients means that clinicians in routine clinical practice have employed strategies used for non-HER2 over-expressing cancers (such as single-agent chemotherapies which do not target HER2), or have empirically substituted one chemotherapy agent with another while continuing trastuzumab. This latter approach is based on limited clinical evidence and local variations in practice occur. The existence of a number of non-randomised studies investigating the continuation of trastuzumab in this way and UK market research data demonstrating use in this setting (Appendix 9.4) suggest, however, that this is a genuine treatment decision which is understandable in light of the lack of alternative options.

As discussed in Section 2.6, brain metastases are an increasing clinical problem in patients with HER2+ breast cancer and represent a significant source of morbidity and mortality (Lin 2007; Patel 2007). The prognosis of patients with untreated brain metastases is very poor yet treatment options are limited. Conventional treatment has been whole brain radiation therapy (WBRT) which has been associated with significant neurocognitive deficits (Patel 2007). Historically, approximately 6-16% of women with metastatic breast cancer developed clinically apparent brain metastases (Lin 2004). However, 28-43% of patients receiving trastuzumab in the metastatic setting have been reported to relapse with brain metastases (Bendell 2003; Lin 2004). This apparent increase may reflect the biology of HER2+ tumours and the inability of trastuzumab, a monoclonal antibody, to cross the blood-brain barrier (Burstein 2005; Lin 2007; Stemmler 2006). Hence, while trastuzumab effectively controls non-CNS disease, the CNS becomes a ‘sanctuary site’ (Clayton 2004; Lin 2007). Interestingly, in the absence of alternative HER2-targeted therapies, trastuzumab is often continued in patients who develop metastases only in the CNS in order to control their extracranial disease (Kirsch 2005). In conclusion, management of breast cancer with brain metastases remains an elusive clinical challenge, and clearly, new and more effective treatment options are greatly needed.

4.6. Provide details of any relevant guidelines or protocols.

NICE has published breast cancer service guidance for England and Wales (NICE Guidance on Cancer Services 2002). Breast cancer service guidance is also available in Scotland (SIGN 2005). NICE is developing a clinical guideline for advanced breast cancer, which is due to be published in January 2009.

NICE Technology Appraisals are available for trastuzumab, capecitabine (NICE TA no.62), vinorelbine (NICE TA no. 54), taxanes (NICE TA no. 30) and gemcitabine (NICE TA no. 116) in advanced or metastatic breast cancer. It is important to note that other than the trastuzumab guidance (NICE TA no.34), none of these specifically address the HER2+ population.

5. Clinical evidence

5.1. Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided.

A systematic review was carried out to identify, report and if appropriate meta-analyse or indirectly compare any studies of relevance to this NICE appraisal. The patient population considered had HER2-positive (HER2+) advanced or metastatic breast cancer and prior treatment including trastuzumab, in line with the proposed SmPC for lapatinib.

Background to the systematic review

This review was initiated in late 2006, prior to the confirmation of scope and decision problem, and therefore had to be sufficiently broad to realistically account for data relevant to the likely licensed indication of lapatinib. Scoping searches identified only one head-to-head randomised controlled trial of lapatinib (EGF100151). A broader search for prospective studies therefore followed, including non-randomised studies, non-comparative studies and studies with an observational design. Treatments included in the initial search strategy were lapatinib, capecitabine, trastuzumab, gemcitabine, vinorelbine, docetaxel and paclitaxel. Research databases and conference proceedings were searched for studies containing these therapies using the strategies outlined in Appendix 9.2.

Following publication of the final scope and GSK's submission of the decision problem, only the following regimens were determined as relevant to this review (restricted comparator list):

- Lapatinib regimens
- Capecitabine monotherapy
- Vinorelbine monotherapy
- Trastuzumab monotherapy
- Trastuzumab plus capecitabine
- Trastuzumab plus vinorelbine
- Trastuzumab plus non-specified or mixed single-agent chemotherapies

The studies retrieved from the initial search were reviewed to determine whether they were relevant to the restricted comparator list. Due to the lack of data for trastuzumab regimens, studies including trastuzumab plus non-specified or mixed single-agent chemotherapies were also included as relevant.

Given the sparseness of data available in this setting, it was also considered important to include retrospective studies. Therefore, those studies initially excluded from the database search were systematically reviewed to find and include relevant retrospective studies.

Database searches were rerun on 28th February for both prospective and retrospective studies with the restricted comparator list (listed above), and the review was updated. Full details of the databases searched and search strategies employed (together with their findings) are provided in Appendix 9.2.

Summary of the final approach

A summary of the final approach is described here.
The following databases were examined from 1985 up to the end of February 2007.
Medline
Medline in process

Embase
Central (CCTR)
CINAHL
Zetoc (conference proceedings)
ISI science and technology (conference proceedings)

The search strategies for the Medline, Embase, CINAHL and Central databases were developed by combining a list of clinical keywords and medical subject headings. The search strategies used for each database are shown in Appendix 9.2. The basic search strategy was as follows: (advanced or metastatic breast cancer) + (any of the comparators) + (HER2 or trastuzumab).

The following conference proceedings were hand searched for the years 2004 - 2006:

- ASCO (American Society of Clinical Oncology)
- ECCO (European Cancer Conference)
- ESMO (European Society for Medical Oncology)
- EORTC-NCI-AACR
- European Breast Cancer Conference
- SABCS (San Antonio Breast Cancer Symposium)
- St Gallen Breast Cancer Meeting

Hand-searching was restricted to the identification of prospective studies, whilst the database searches included the identification of retrospective studies, as well as prospective studies.

Further details on the conduct of the systematic review can be found in Appendix 9.2 and full eligibility criteria of studies included in the final review are described in section 5.2.

5.2. Study selection

Two randomised controlled trials (RCT) (EGF100151; Miller 2005), meeting the inclusion criteria for the systematic review, were identified. EGF100151 is the pivotal registration trial of lapatinib plus capecitabine versus capecitabine alone that forms the basis of this submission. The RCT by Miller et al (Miller 2005) compares a non-relevant intervention (bevacizumab* plus capecitabine) with capecitabine alone in a population that was not limited to HER2+ patients. Therefore, only the capecitabine arm of this study has been considered and is presented in section 5.8 as non-RCT evidence.

*Avastin® (Roche) – Unlicensed in combination with capecitabine in relapsed metastatic breast cancer. Received EU marketing authorisation March 2007 for first-line treatment of metastatic breast cancer in combination with paclitaxel.

5.2.1. Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors. Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and /or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Interim data (with a cut-off date of 15 November 2005) from the single relevant RCT [EGF100151] comparing the intervention (lapatinib plus capecitabine) with capecitabine monotherapy were presented at ASCO 2006 (Geyer 2006a), ESMO 2006 (Cameron 2006a), SABCS 2006 (Cameron 2006b) and published in the New England Journal of Medicine (Geyer 2006b).

The efficacy and safety data presented in this submission reflect that reported in the GlaxoSmithKline (GSK) Clinical Study Report (CSR, ZM2006/00137/00) for patients enrolled as of 03 April 2006 cut-off (provided to NICE with this submission). A follow-up publication reflecting this later data set is anticipated in June 2007. Data collection from the study is still ongoing for further analyses. Analyses of health outcomes data for the 03

April 2006 dataset are available in a separate study report (available to NICE and the ERG on request).

5.2.2. Inclusion and exclusion criteria for systematic review

State the inclusion and exclusion criteria that were used to identify the studies detaild in the list of relevant RCTs.

Only publications in English were considered and to be included in the systematic review, trials had to meet the eligibility criteria listed below. The rationale for the application of these inclusion criteria was the target-licensed indication for lapatinib, the context of the decision problem, the NICE scope and potential comparators in routine clinical practice in the UK.

Initial pre-decision problem criteria:

Study design:

- prospective
- randomised or non-randomised
- controlled or uncontrolled
- observational (except case studies)

Patients:

- refractory advanced or metastatic breast cancer with stage IIIB / stage IIIC with T4 lesion, or stage IV disease.
- HER2+

Prior therapy:

- to include trastuzumab and either an anthracycline or a taxane*
- at least one line of therapy in the metastatic setting

Relevant therapy:

- Each included trial had to include at least one of the following treatments: lapatinib, capecitabine, trastuzumab, gemcitabine, vinorelbine, docetaxel, paclitaxel.
- Comparator treatments to lapatinib could have been placebo, best supportive care or any of the above.

Post-decision problem criteria (as above but with the following changes):

Study design:

- Both retrospective and prospective studies included

Prior therapy:

- No requirement for prior anthracycline or taxane therapy for retrospective studies**
- At least one line of therapy in the metastatic setting (this therapy was required to be trastuzumab for any trastuzumab-containing comparator)

Relevant therapy:

- Lapatinib regimens
- Capecitabine monotherapy
- Vinorelbine monotherapy
- Trastuzumab monotherapy
- Trastuzumab plus capecitabine
- Trastuzumab plus vinorelbine
- Trastuzumab plus non-specified or mixed single-agent chemotherapy

Notes:

* While the EGF100151 study required prior treatment with both an anthracycline and a taxane (as well as prior trastuzumab), the criteria were relaxed for the systematic review to include studies in which patients could have received either an anthracycline **or** a taxane. This was because scoping searches identified very few studies in which all patients had received prior treatment with both agents, in addition to trastuzumab.

** No prospective studies were excluded solely on the basis of not meeting the requirement for prior therapy with either an anthracycline or a taxane (as well as prior trastuzumab) i.e. no otherwise relevant studies were found where patients had previously received trastuzumab but

neither an anthracycline nor a taxane. This requirement was removed for the retrospective studies given the high likelihood that included patients would have previously received at least one of these therapies.

Citations and data from the initial search that are not relevant to the decision problem are included in Appendix 9.7.

5.2.3. List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem.

See 5.2.1. EGF100151 is the only relevant RCT identified by the systematic review.

5.2.4. List of relevant non-randomised controlled studies

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem.

Non-randomised, non-controlled studies identified by the review are discussed in section 5.8.

5.2.5. Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

The following table details only those ongoing studies of lapatinib in patients with advanced or metastatic breast cancer who have received prior treatment with trastuzumab i.e. relevant to the population under consideration in this submission.

Table 5.1: Ongoing studies of lapatinib in patients with advanced or metastatic breast cancer who have received prior treatment with trastuzumab

Study	Location	Phase / Design	Setting	Target Patient Numbers	Interventions	Primary endpoint	Status
EGF104900	Global (incl. UK centres)	Phase III, open-label RCT	Patients with HER2+ advanced or metastatic breast cancer previously treated with trastuzumab for metastatic disease, and an anthracycline and taxane	270	Lapatinib 1000mg/day + trastuzumab 2mg/kg/week vs. lapatinib 1500mg/day	PFS	Enrolment completed Results expected 2H 2007
EGF105084	Global (incl. UK centres)	Phase II, open-label	Patients with progressive CNS metastases from HER2+ metastatic breast cancer; previously treated with trastuzumab and cranial radiotherapy / radiosurgery	220	Lapatinib 750mg b.d.	Objective response rate in CNS	Enrolment completed Results expected 2H 2007
EGF103659* **Lapatinib Expanded Access programme (EAP)**	Global (incl. UK centres)	Expanded Access programme	Patients with HER2+ advanced or metastatic breast cancer previously treated with trastuzumab for metastatic disease, and an anthracycline and taxane	-	Lapatinib 1250mg/day + capecitabine* 2000 mg/m^2/day on days 1-14 of a 3-week cycle	Potential Clinical Benefit	Ongoing
EGF107671*	Global (incl. UK centres)	Phase II, open-label, parallel-group	Patients with progressive CNS metastases from HER2+ metastatic breast cancer; previously treated with trastuzumab and cranial radiotherapy / radiosurgery	110	Lapatinib 1250mg/day + topotecan 3.2mg/m^2 on days 1, 8, and 15 of 4-week cycle *Or* Lapatinib 1250mg/day + capecitabine 2000mg/m^2 on days 1-14 of 3-week cycle	Objective response rate in CNS	Due to start March 2007

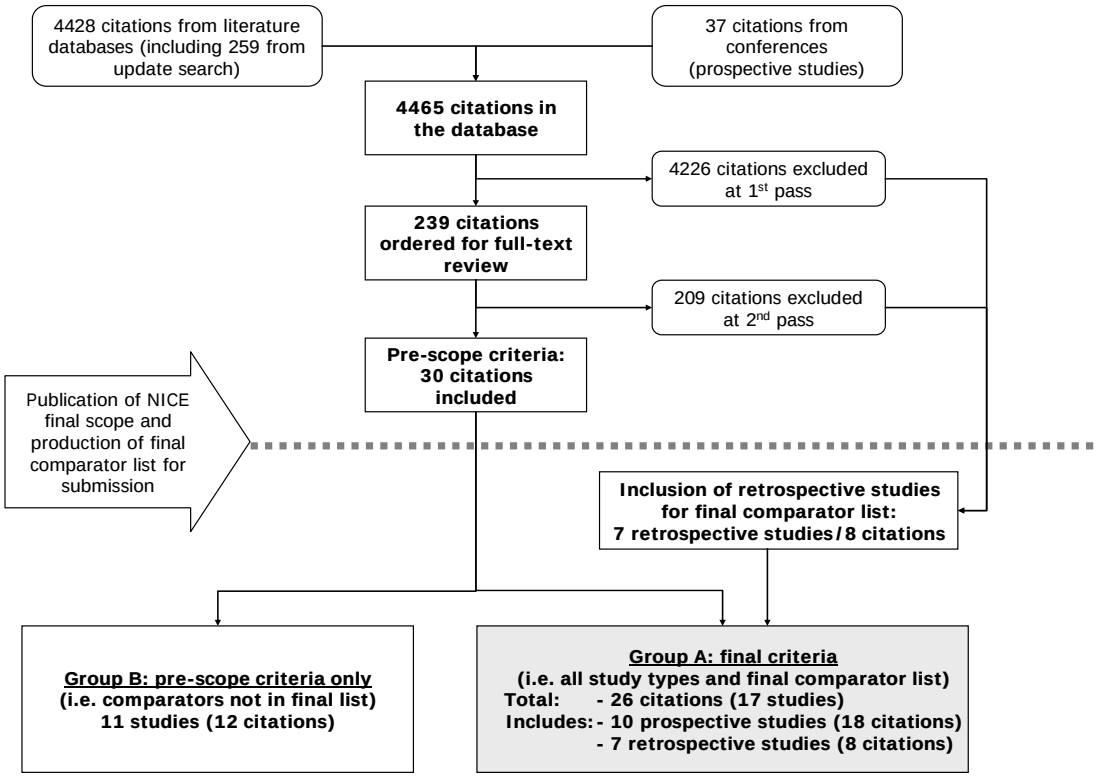
Study	Location	Phase / Design	Setting	Target Patient Numbers	Interventions	Primary endpoint	Status
EGF104911	Japan	Phase II, open-label	Patients with HER2+ advanced or metastatic breast cancer refractory to treatment with trastuzumab for metastatic disease, and an anthracycline and taxane	52	Lapatinib 1500mg/day	Tumour response	Ongoing
EGF100642	Japan	Phase II, open-label	Patients with HER2+ advanced or metastatic breast cancer previously treated with trastuzumab for metastatic disease, and an anthracycline and taxane	52	Lapatinib 1500mg/day	Tumour response	Ongoing
EGF105635	Japan	Phase I / II, open-label	Patients with HER2+ advanced or metastatic breast cancer previously treated with trastuzumab	22	Lapatinib 750 or 1000 mg daily + trastuzumab	Phase I: Optimal tolerated dose. Phase II: Tumour response	Ongoing

* Study includes lapatinib plus capecitabine regimen for which market authorisation has been sought

5.2.6. Flow diagram

Studies were included/excluded on the basis of explicit criteria described in section 5.2.2 and the results of each stage of the inclusion/exclusion process are summarised below in Figure 5.1. There was a very large number of excluded trials, the details of which are available upon request.

Figure 5.1: Flow diagram of included/excluded studies.



Note: The number of included citations reflects multiple publications from the same trial. In addition to the citations retrieved by the literature search, 4 Clinical Study Reports (CSRs) for lapatinib trials were also identified [EGF100151 (15 Nov 2005 cut-off); EGF100151 (03 April 2006 cut-off); EGF20002; EGF200080].

5.3. Summary of methodology of relevant RCTs

Study EGF100151 was the single RCT identified as fulfilling the inclusion criteria for this review.

5.3.1. Methods

Describe the RCT design (for example, duration, degree and method of blinding and randomisation)

This was a phase III randomised, open-label, multi-centre, parallel-group study to evaluate and compare the treatment of lapatinib plus capecitabine versus capecitabine alone when administered to women with HER2+ advanced or metastatic breast cancer who had received prior therapy which included anthracyclines, taxanes and trastuzumab. Trastuzumab must have been administered for at least 6 weeks in the locally advanced/metastatic setting, but may also have been given in the adjuvant setting.

Blinding

This was an open-label study due to the difficulty in blinding the treatment of two different doses of capecitabine and the additional complexity of capecitabine being supplied in 150 and 500mg tablets which were taken in different combinations to achieve the required dose by body surface area.

In view of the open-label nature of the study, all objective evidence (e.g. radiological scans and medical photographs) from all patients, whether or not the investigator had reported progression, underwent review by the Independent Radiological Review Committee (IRC), blinded to treatment and the investigator-determined outcome, to determine response and progresion. An independent statistician performed the analysis of the data that was then submitted to the Independent Data Monitoring Committee (IDMC) for review.

In addition, personnel involved in the conduct and analysis of the study within GSK remained blinded to the subjects' treatment until after the clinical database had been locked.

Randomisation

Allocation was concealed through use of an interactive voice response (IVR) system for randomisation of patients. Patients were assigned to receive lapatinib plus capecitabine or capecitabine alone in accordance with the computer-generated randomisation schedule. Randomised patients were identified by a unique subject number assigned for the duration of the study. Randomisation was stratified according to three categories based on stage and site of disease:

Disease stage IIIB or IIIC, with T4 lesions
Disease stage IV / visceral site (any visceral site)
Disease stage IV / non-visceral site.

Duration

Treatment was administered until disease progression or withdrawal from the study was required due to unacceptable toxicity or other reasons (e.g. consent withdrawal). Patients who were withdrawn from the study but who had not progressed were followed-up until disease progression and then at approximately 12-week intervals until death for survival analyses.

Dosing

Patients received either lapatinib 1250mg once daily on a continuous basis plus capecitabine 2,000mg /m2 on days 1-14, of a 21-day treatment cycle or capecitabine 2,500mg/m2 alone on days 1-14, of a 21-day treatment cycle. Subjects were instructed to

take lapatinib at least one hour before or one hour after breakfast. Capecitabine was taken in two divided doses, 12 hours apart, either with food or 30 minutes after food.

The optimally tolerated regimen (OTR) for the lapatinib plus capecitabine combination was established in a phase I study (EGF10005) (De Bono 2003; Schwartz 2004). Dose limiting toxicities (DLTs) of diarrhoea and rash occurred at dose combinations of lapatinib 1500mg daily plus capecitabine 2000mg/m2/day and lapatinib 1250mg daily plus capecitabine 2500mg/m2/day. The OTR was therefore defined as lapatinib 1250mg daily plus capecitabine 2000mg/m2/day. The 2500mg/m2 dosage in the capecitabine monotherapy arm was based on the recommended dosage in the capecitabine SmPC (Xeloda® SmPC).

Details of guidance on dose delays / dose reductions in order to manage toxicity are provided in the CSR. Subjects who experienced 'unacceptable toxicity' were discontinued permanently and withdrawn from the study.

Prohibited medications

Lapatinib is predominantly metabolised by CYP3A4. Concomitant medications that are either inducers or inhibitors of CYP3A4 were prohibited. The use of medications/ substances contra-indicated with capecitabine was not permitted. Full details of other prohibited medications can be found in the study protocol (available to NICE on request).

5.3.2. Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

Patients were eligible for inclusion in the trial if they had HER2-overexpressing advanced or metastatic breast cancer and had received prior therapy with trastuzumab in the advanced/metastatic setting, as well as an anthracycline and a taxane as either adjuvant treatment or for metastatic disease.

5.3.2.1. Main inclusion criteria:

- Adult females of at least 18 years of age
- Histologically confirmed invasive breast cancer with stage IIIb / stage IIIc with T4 lesion, or stage IV disease
- Documented HER2 over-expression (IHC 3+ or IHC 2+ with FISH confirmation)
- Documented progressive advanced or metastatic breast cancer (defined as appearance of any new lesion not previously identified or increase of > 25% in existent lesions, and must be documented)
- Refractory breast cancer, defined as progression in the locally advanced or metastatic setting, or relapse within 6 months of completing adjuvant therapy
- Prior therapies must have included, but not been limited to, at least 4 cycles of regimens containing an anthracycline and a taxane (2 cycles if the disease progressed while the women were receiving therapy), administered concurrently or separately in the adjuvant or metastatic setting
- Prior treatment must have contained trastuzumab alone or in combination with other chemotherapy for at least 6 weeks in the advanced/metastatic setting
- No prior capecitabine
- Subjects with hormone-receptor positive tumours must have had disease progression following hormone therapy, unless intolerant to hormonal therapy or hormonal therapy was not considered to be clinically appropriate
- Subjects with stable CNS metastases were eligible if they were clinically stable (asymptomatic and off systemic steroids and anticonvulsants for > 3 months)
- ECOG Performance Status of 0 (fully active, able to carry on all pre-disease performance without restriction) or 1 (restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature)
- Measurable disease according to modified RECIST criteria

- Life expectancy of at least 12 weeks
- Cardiac ejection fraction within institutional range of normal as measured by echocardiogram (MUGA scan may have been performed if ECHO was not available)
- Adequate renal, hepatic and haematological functions.

5.3.2.2. Main exclusion criteria:

- Known history of uncontrolled or symptomatic angina, arrhythmia or congestive heart failure
- Prior treatment with anti-EGFR (ErbB1) or HER2 (ErbB2) inhibitors for breast cancer other than trastuzumab
- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery immunotherapy, biologic therapy, or tumour embolisation) other than capecitabine
- Hypersensitivity to the active agents.

5.3.2.3. Baseline demographic and disease characteristics

The two treatment groups were very well matched in terms of demographic and disease characteristics (see Table 5.2). Anthracyclines, taxanes and trastuzumab were recorded as prior therapies for ≥ 98% of patients, with ≥ 95% of trastuzumab use in the metastatic setting. Time since last dose of trastuzumab to randomisation was very similar in both groups.

Table 5.2: Baseline demographic and disease characteristics in study EGF100151 (03 April 2006 cut-off)

		Lapatinib plus capecitabine (n=198)	**Capecitabine** (n=201)
Age (years)	Mean (SD)	53.6 (10.5)	51.2 (10.3)
	Median (range)	54 (26-80)	51 (28-83)
ECOG performance status	0	103 (58%)	104 (60%)
	1	71 (40%)	66 (38%)
	unknown	3 (2%)	3 (2%)
Baseline disease stage	Stage IV visceral	148 (75%)	158 (79%)
	Stage IV non-visceral	43 (22%)	35 (17%)
	Stage IIIb or IIIc with T4 lesion	7 (4%)	8 (4%)
Hormone receptor status	ER+ and/or PR+	96 (48%)	93 (46%)
	ER- and/or PR-	99 (50%)	107 (53%)
	Unknown	3 (2%)	1 (<1%)
Number of metastatic sites	≥ 3	98 (49%)	96 (48%)
	2	61 (31%)	61 (30%)
	1	39 (20%)	44 (22%)
Metastatic Sites* *Unknown for 1 patient	Visceral Only	33 (17%)	36 (18%)
	Visceral / Non-visceral	120 (61%)	122 (61%)
	Non-visceral only	45 (23%)	43 (21%)
Prior anthracyclines		194 (98%)	199 (>99%)
Prior taxanes		198 (100%)	199 (>99%)
Prior trastuzumab		196 (99%)	197 (98%)
Weeks since last trastuzumab administered	< 6 weeks	98 (50%)	98 (50%)
	6-12 weeks	37 (19%)	38 (19%)
	> 12 weeks	61 (31%)	58 (29%)
	Missing	-	3 (2%)
Trastuzumab exposure (weeks)	Mean (SD)	57.2 (48.2)	59.3 (49.3)
	Median (range)	43.6 (3-296)	45.3 (0-329)
Intent of trastuzumab	Adjuvant	9 (5%)	7 (4%)
	Metastatic	187 (95%)	189 (96%)
	Neo-adjuvant	0	1 (1%)
Progressed on trastuzumab for metastatic cancer		182 (97%)	185 (98%)

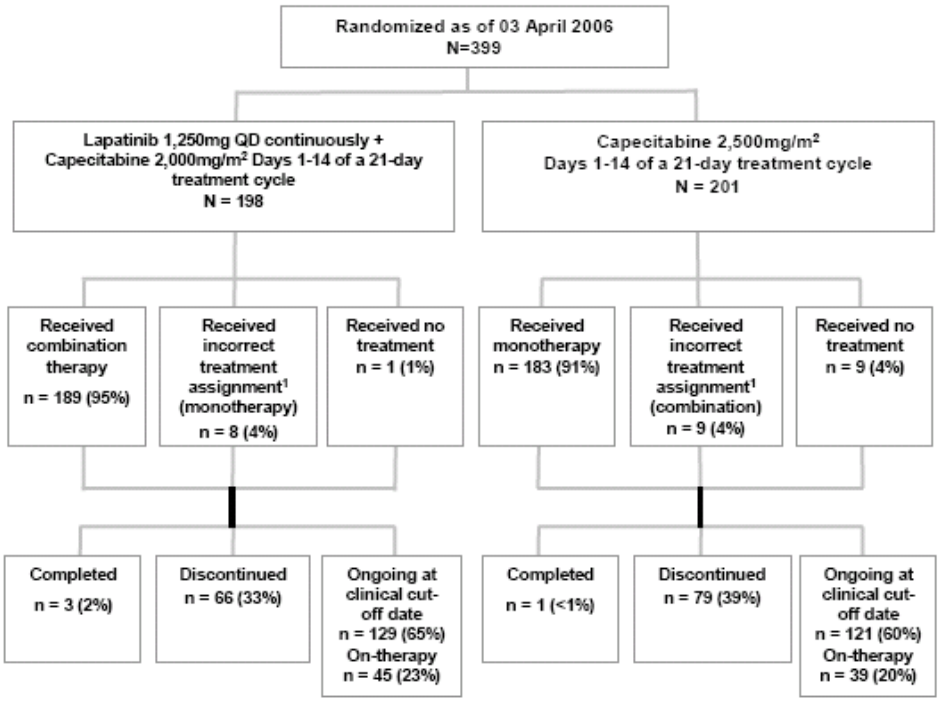
5.3.3. Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow-up withdrew from the RCT. This information should be presented as a CONSORT flow chart.

A recruitment target of 528 patients was planned for the study. A pre-specified interim analysis of the primary endpoint (Time to Progression, TTP) was to be conducted after approximately 133 independent time-to-progression events (later adjusted to account for possible differences between investigator and independent review, allowing 146 investigator-reported events).

A clinical cut-off date of the 15 November 2005 was chosen for the interim analysis. As of this date, 146 investigator-identified progression events had been reported in 324 patients. On 20 March 2006 after a review of the findings, the IDMC unanimously recommended that, for ethical reasons, study enrolment be halted based on the clinically meaningful, statistically significant advantage in TTP for the lapatinib plus capecitabine arm versus capecitabine alone.

Figure 5.2: Subject Disposition (ITT) population (03 April 2006 cut-off)



1. 17 subjects did not receive therapy assigned by randomization due to a transient randomization issue, which resulted in an incorrect notification of an assigned treatment.(8 patients in the combination arm received monotherapy, 9 patients in the monotherapy arm received combination treatment.). In the Safety Population, these 17 subjects were assigned to the treatment actually received.

Note: The ITT populations included patients in the treatment groups to which they had been randomised. In error, 4% of patients randomised to the combination arm received capecitabine alone and 4% of patients randomised to the monotherapy arm received combination treatment. Any influence that this incorrect treatment allocation may have on results for the ITT population is likely to be in the direction of an under-estimation of the effectiveness of lapatinib plus capecitabine compared with capecitabine alone.

A total of 399 patients were enrolled in the study (lapatinib plus capecitabine N=198; capecitabine alone N=201) at termination of enrolment on 03 April 2006. The majority (63%) were still on study drug or being followed up for survival. Women receiving

capecitabine alone were offered the option of switching to lapatinib plus capecitabine and continuing in the study; 33 of 39 patients on capecitabine monotherapy who had not progressed were switched to receive combination therapy.

The proportion of patients withdrawing from the study and the reasons for study withdrawals were similar between treatment groups. The primary reason for discontinuing study medication was disease progression (lapatinib + capecitabine: 114/153, capecitabine 119/152).

5.3.4. Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including detail of length of follow-up. Timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

Efficacy assessments were performed every 6 weeks for the first 24 weeks and then every 12 weeks while patients were receiving study treatment. There were additional safety assessments performed on all patients every 3 weeks and at the end of treatment. Patients withdrawn from the study who had not progressed were assessed every 12 weeks until progression and then followed up at approximately 12-week intervals for survival analysis.

5.3.4.1. Description of efficacy endpoints

Primary endpoint

- Time to progression (TTP)

Time to progression (TTP), defined as the interval between the date of randomisation and the earliest date of either disease progression or death due to breast cancer as assessed by the IRC under blinded conditions, was defined *a priori* as the primary endpoint for this study.

TTP was selected as the primary endpoint as being an appropriate and sensitive parameter to assess treatment benefit in patients with advanced/metastatic disease. (Di Leo 2003) It is considered by clinical oncologists and regulators to be a valid surrogate for overall survival in this setting (EMEA 2005).

An improvement in TTP is of clinical benefit, and has been shown to correlate with an increase in overall survival in metastatic breast cancer (Sherrill 2007). Meta-regression analyses of 68 RCTs in metastatic breast cancer, identified by a systematic review, indicate that a delay in time to progression results in an increase in survival by at least a commensurate amount, with the benefit of additional survival seeming to occur prior to progression. In a subset analysis of a small number of studies conducted entirely in a HER2+ population, there was evidence for a survival difference between groups greater than the difference seen in TTP (RTI Health Solutions report for GSK, data on file).

Assessments of endpoints by an independent review committee under blinded conditions are a robust assessment and more impartial than those conducted by investigators. Hence, it is entirely reasonable that the independently-assessed TTP rather than the investigator-assessed TTP should have formed the primary endpoint.

Secondary endpoints included:

- Overall survival (OS) – the time from randomisation until death due to any cause
- Progression-free survival (PFS) – the time from randomisation until the first documented sign of disease progression or death due to any cause. Thus, the difference between TTP and PFS was that the latter included death from any cause rather than just breast cancer.
- 6-month progression-free survival – the percentage of surviving subjects who were progression-free 6 months (183 days) after the date of randomisation
- Overall tumour response rate (ORR) – the percentage of subjects achieving either a complete response (CR) or partial response (PR)
- Clinical benefit rate (CBR) – the percentage of subjects with evidence of CR or PR or stable disease (SD) for at least 6 months (183 days)
- Duration of response – the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to breast cancer.

The incidence of brain metastases as a first site of relapse was examined in a post-hoc analysis.

For the analyses of TTP, PFS, ORR, and CBR, copies of serial radiographs and photographs of visible lesions used for efficacy determinations were collected for independent assessment under blinded conditions. Supportive analyses of these endpoints were conducted with the investigator-reported assessments.

The internationally recognised RECIST (Response Evaluation Criteria in Solid Tumours) was used to denote measurable disease and its progression (Therasse 2000). Measurable disease was defined by the presence of at least one measurable lesion. A measurable lesion was one that could be accurately measured in at least one dimension (longest diameter) of:

- 15mm with conventional techniques (medical photograph, palpation, plain X-ray, CT or MRI) or > 10mm with spiral CT scan.

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all lesions involved, were identified as target lesions and recorded and measured at baseline. A sum of the longest diameter (LD) of all target lesions was calculated and reported as the baseline sum LD, which was used as a baseline by which to characterise objective tumour response. All other lesions (and sites of disease) were identified as non-target lesions.

Definitions for assessments of response were:

- Complete Response (CR) – disappearance of all target lesions.
- Partial Response (PR) – at least a 30% decrease in the sum of the longest diameter (LD) of the target lesions, taking as a reference the baseline sum LD.
- Stable Disease (SD) – neither sufficient shrinkage to qualify for a PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum LD since the treatment started.
- Progressive Disease (PD) – at least a 20% increase in the sum of the LD of target lesions, taking as reference, the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions.
- Not Evaluable (NE)

5.3.4.2. Safety Assessments

Safety assessments included:

- Adverse events (AE)*
- Serious adverse events (SAE)
- Physical examination
- Clinical laboratory evaluations (haematology evaluations, liver function tests)
- Vital signs

- Electrocardiogram (12-lead ECG)
- Echocardiogram (ECHO) (or MUGA scan)

The investigator was responsible for the detection and documentation of events meeting the criteria and definition of an AE and an SAE.
* The intensity of AEs was assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0).

5.3.4.3. Health outcomes assessments

Changes in quality of life were assessed relative to baseline using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire and the Euro QOL (EQ-5D) questionnaire. The protocol required patients to complete questionnaires at scheduled visits at baseline, every 6 weeks for the first 24 weeks, and every 12 weeks thereafter until discontinuation of study treatment, when patients completed questionnaires at their "concluding visit".

The FACT-B consists of FACT-General (FACT-G) plus a breast cancer subscale specific to quality of life in breast cancer. This 37-item, self-reporting questionnaire consists of 5 subscales (physical well-being, social/family well-being, emotional well-being, functional well-being, and breast cancer subscale). Subscale scores are used to generate 3 summary scores – FACT-B total score (range 0-144), FACT-G total score (range 0-108) and Trial Outcome Index (TOI) (range 0-92). For all scores/scales, the higher the score, the better the quality of life.

The EQ-5D questionnaire comprises a visual analogue thermometer (rated 0 to 100) and a multi-attribute health status measure. A UK-specific tariff was applied to data from the latter to attach utilities to health states reported in the study (Dolan 1997).

5.3.4.4. Compliance

Compliance with both lapatinib and capecitabine dosing was assessed by querying the patient during site visits. A record of the number of lapatinib and/or capecitabine tablets dispensed to and returned by the subject at each visit was recorded in the Case Record Form (CRF).

5.3.5. Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analyses used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

5.3.5.1. Hypotheses

The study was designed to provide evidence to support the null hypothesis H_0: $\lambda \geq 1$ or to reject it in favour of the alternative hypothesis H_A: $\lambda < 1$, where λ is the hazard ratio for TTP: lapatinib + capecitabine / capecitabine alone.

5.3.5.2. Sample size

A total of 266 TTP events were calculated as being required to achieve a statistical power of 90% to detect a 50% increase in the median TTP (from an estimated 3 months in the group receiving capecitabine alone to 4.5 months in the group receiving lapatinib plus capecitabine). An analysis of overall survival was to be performed after 457 deaths had occurred, giving a statistical power of 80% to detect a 30% increase in median survival (from 8 months in the monotherapy group to 10.4 months in the combination group). To meet these requirements, an enrolment of 528 patients was planned.

5.3.5.3. Analyses

For TTP, two analyses were planned. The protocol specified that an interim analysis was to be conducted after approximately 133 independently-assessed disease progression events (later adjusted to account for possible differences between investigator and independent review, allowing 146 investigator-reported events). The final analysis would occur after 266 independently-assessed events. O'Brien-Fleming stopping boundaries with one-sided 2.5% significance level were used to reject either H_0 or H_A.

5.3.5.4. Data monitoring

An IDMC was set up to review accumulating safety and efficacy data and to provide an opportunity to terminate the study early if:

- there were concerns regarding safety
- there was strong evidence of superior efficacy of lapatinib plus capecitabine
- there was strong evidence that lapatinib plus capecitabine would fail to show superiority if the study was allowed to run to planned completion.

Following review of the interim data, the IDMC found evidence of superior efficacy for lapatinib plus capecitabine, and unanimously recommended termination of study enrolment.

5.3.5.5. Analysis populations

- The Intention-to-Treat (ITT) population comprised all randomised subjects and was used for the analysis of efficacy data. Note: this population is used in the economic analyses for this submission.
- The Safety Population comprised all randomised subjects who received at least one dose of randomised therapy and was used for analysis of the safety data.
- A supplementary per-protocol analysis (comprising all randomised and treated subjects who complied closely with the protocol) was also conducted for TTP.

5.3.5.6. Strata and covariates

Randomisation was stratified according to stage of disease and site of disease (visceral/non-visceral). The three possible strata were:

- Stage IIIB or IIIC, with T4 lesion
- Stage IV / Visceral
- Stage IV / Non-visceral

In all efficacy analyses, significance tests were stratified by stage of disease and site of disease.

5.3.5.7. Examination of subgroups

The only prospectively defined subgroups for conducting analyses were age group (< 65 years, $\geq$65 years) and race (White, Black, Asian, American Hispanic, other).

5.3.5.8. Multiple comparisons/multiplicity

There were no adjustments for multiplicity.

5.3.5.9. Censoring

For patients in whom progressive disease was not confirmed by independent review and who had not died at the time of the analyses, TTP, PFS, and duration of response were censored at the date of the last independent assessment and before the initiation of any alternative anticancer therapy. For patients who had not died at the time of the analysis, time to death (Overall Survival) was censored at the time of last contact. For subjects

who withdrew from the study with no tumour response, time to response was censored at the time of study withdrawal. Further information on censoring can be found in the study protocol and CSR.

5.3.5.10. Other considerations for data analysis

Withdrawals and missing data
All withdrawals were included in analyses up to the time of withdrawal. Patients who were withdrawn prematurely from study drug but who were not withdrawn from the study at the same time were included in all analyses regardless of the duration of treatment. For endpoints which determined percentage of responders, subjects with unknown or missing response data were treated as non-responders.

Overall survival
As described above, the study was originally powered to detect a statistically significant difference in OS (secondary endpoint) between treatment groups. However, because study enrolment was halted early and patients offered the option of crossing over to combination therapy, it is unlikely that there will now be sufficient power to confirm a significant difference in overall survival. Modelling / extrapolation of the OS estimates has therefore been necessary for the health economic analyses (Section 6.2.6).

5.3.6. Critical appraisal of relevant RCTs

Each RCT should be critically appraised.

The critical appraisal for study EGF100151, based on the protocol and CSR is provided in Table 5.3.

Table 5.3: Critical appraisal checklist for study EGF100151

EGF100151	
Critical Appraisal Criterion	**Assessment**
How was allocation concealed?	Open-label study. However, after enrolling a patient into the study but prior to contacting the interactive voice response (IVR) system (RAMOS – Registration and Medication Ordering System), study investigators were unaware of the treatment group assignment for each patient (see below).
What randomisation technique was used?	Subjects were assigned a unique subject number allocation. To randomise the subject, the study staff contacted RAMOS and entered the subject's number, stage of disease and sites of disease to obtain a computer-generated randomisation number and treatment group assignment. Subjects were randomised in permuted blocks of six within strata defined according to disease stage and the presence or absence of visceral metastases.
Was a justification of the sample size provided?	Yes. The sample size was calculated to be able to detect a significant difference in both TTP and OS between treatment groups.
Was follow-up adequate?	Yes. Subjects were followed-up until death unless lost to follow-up.
Were the individuals undertaking the outcomes assessment aware of allocation?	Investigators/study staff were aware of allocation. A blinded IRC reviewed all objective evidence (e.g. radiological scans and medical photographs from all patients whether or not the investigator had reported progression) to determine response and progression. An independent statistician performed the analysis of the data that was then submitted to IDMC for review. Primary endpoint was based on the independently-assessed TTP.
Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.	Parallel-group. After study enrolment was halted, patients in capecitabine monotherapy group were offered the option of crossing-over to lapatinib plus capecitabine.
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	Global study with sites in N. America, S. America, S. Africa, Hong Kong, Australia and Europe, including 12 UK sites which recruited 43 patients (approximately 10% of the total study population). The study was carried out to reflect standard therapeutic practice for the management of relapse metastatic breast

	cancer across the countries in which it was conducted.
How do the participants included in the RCT compare with patients who are likely to receive the intervention in the UK?	Similar. Patients in the RCT were HER2+ and required to have had prior therapy with an anthracycline and a taxane in either the adjuvant or metastatic settings, plus trastuzumab for metastatic disease. This is slightly more restrictive than the likely indication statement which does not stipulate prior trastuzumab in the metastatic setting. The demographic characteristics of the patients in the RCT were representative of the characteristics expected of this population in the UK. The median age of the total RCT population was 52 years which is similar to that seen in a metastatic breast cancer population progressing on trastuzumab in UK clinical practice (median in range 56-60 years, see Appendix 9.4.1.1). The performance status of the RCT and real-life populations are also similar (ECOG PS of 0 or 1).
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Lapatinib 1250mg daily on a continuous basis plus capecitabine 2000mg/m^2 on days 1-14 of a 21-day cycle, versus capecitabine 2500mg/m^2 on days 1-14 of a 21-day. The dosage in the combination arm was based on the OTR identified in a phase I study (EGF10005) and is the proposed SmPC recommendation. The dosage in the capecitabine monotherapy arm is consistent with that recommended on the capecitabine SmPC.
Were the study groups comparable?	Yes.
Were the statistical analyses used appropriate?	Yes.
Was an intention-to-treat analysis undertaken?	Yes.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	Yes. The study was powered at 80% to detect a 30% increase in median survival, which required 457 deaths. However, based on the superior TTP findings at the pre-planned interim analysis, the IDMC recommended halting enrolment and allowed patients receiving capecitabine alone to cross-over to lapatinib plus capecitabine. At the time enrolment was halted there were 399 subjects enrolled and 119 deaths observed; 33 of 39 patients on capecitabine monotherapy who had not progressed were switched to receive combination therapy. Therefore there is a low likelihood that a statistically significant difference in overall survival between treatment groups will be demonstrated.

5.4. Results of the relevant comparator RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem.

Study EGF100151

5.4.1. Primary Efficacy Endpoint

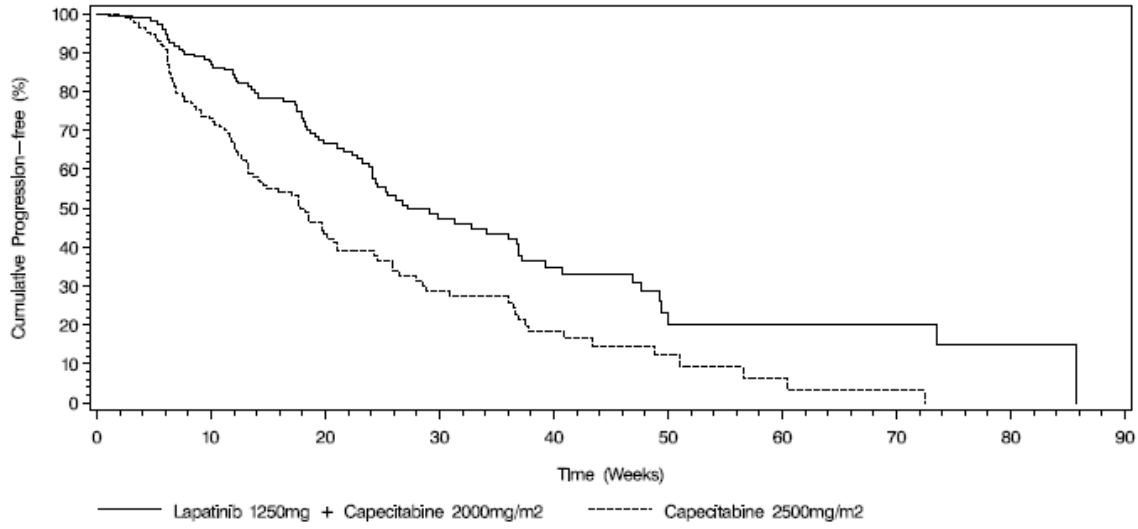
The difference between the treatment groups in the primary endpoint of TTP, based on the blinded assessments by the IRC, was both clinically meaningful and highly statistically significant in favour of the lapatinib plus capecitabine combination (Table 5.4 and Figure 5.3).

Table 5.4: Primary endpoint - TTP (as assessed by independent review, ITT population, 03 April 2006 cut-off)

Outcome Measure	Lapatinib + Capecitabine (N=198)	Capecitabine (N=201)	Hazard Ratio (95% CI)	Log-rank 2-sided p-value
Median TTP (weeks) (95% CI)	27.1 (17.4, 49.4)	18.6 (9.1, 36.9)	0.57 (0.43, 0.77)	0.00013

A per protocol (PP) analysis of the independently-assessed TTP excluding 51 patients found similar results (median TTP of 27.1 weeks in the lapatinib plus capecitabine group vs. 17.6 weeks in the capecitabine group; HR: 0.50, 95% CI: 0.36, 0.68; two sided p=0.000004).

Figure 5.3: Kaplan Meier Estimates of TTP (as assessed by independent review, ITT population, 03 April 2006 cut-off)



5.4.2. Secondary Efficacy Endpoints

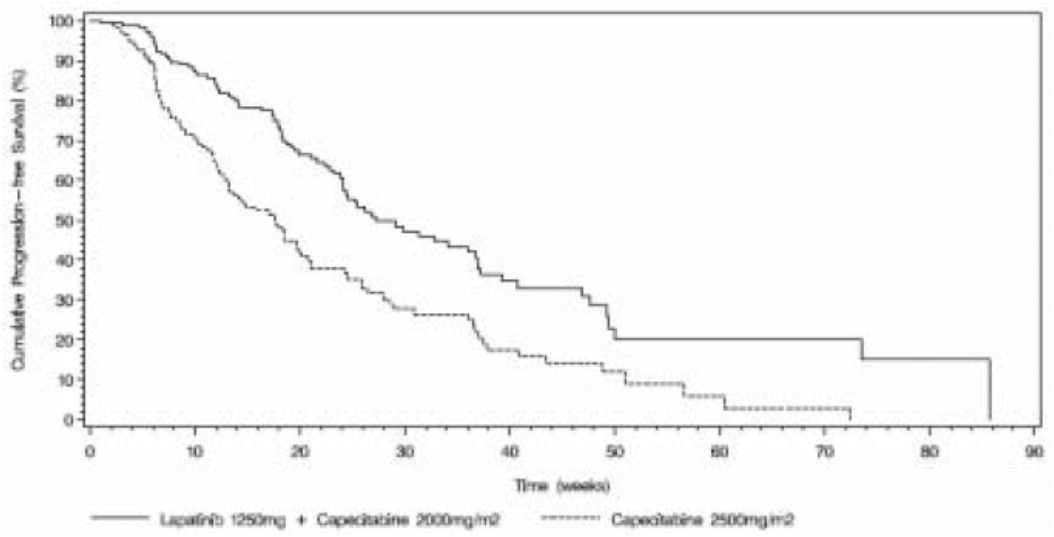
By independent assessment, the differences between treatment groups in progression-free survival and responses rates were statistically significant (Table 5.5). The probability of being progression-free at 6 months was 52% in the lapatinib plus capecitabine group and 33% in the capecitabine monotherapy group (Figure 5.4).

Table 5.5: Secondary endpoint results (as assessed by independent review, ITT population, 03 April 2006 cut-off)

Outcome Measure	Lapatinib + Capecitabine (N=198)	Capecitabine (N=201)	Hazard Ratio (95% CI)	Odds Ratio (95% CI)	Two-sided p-value
Median PFS (weeks) (95% CI)	27.1 (24.1, 36.9)	17.6 (13.3, 20.1)	0.55 (0.41, 0.74)	-	0.000033*
Overall Response Rate (CR or PR) (%) (95% CI)	23.7 (18.0, 30.3)	13.9 (9.5, 19.5)	-	1.9 (1.1, 3.4)	0.017†
Clinical Benefit Response Rate (CR or PR or SD > 6 months) (%)	29.3	17.4	-	2.0 (1.2, 3.3)	0.008†
Median duration of response (weeks)	32.1	30.6	-	-	Not analysed

* Log-rank two-sided p-value
† Exact test two-sided p-value

Figure 5.4: Kaplan Meier Estimates of PFS (as assessed by independent review, ITT population, 03 April 2006 cut-off) [Academic in Confidence]



The differences between treatment groups in the investigator-assessed endpoints were also statistically significant (Table 5.6).

Table 5.6: Secondary endpoint results (evaluated by investigator, ITT population, 03 April 2006 cut-off)

Outcome Measure	Lapatinib + Capecitabine (N=198)	Capecitabine (N=201)	Hazard Ratio (95% CI)	Odds Ratio (95% CI)	Two-sided p-value
Median TTP (weeks) (95% CI)	23.9 (12.0, 44.0)	18.3 (6.9, 35.7)	0.72 (0.56, 0.92)	-	0.00762*
Overall Response Rate (CR or PR) (%) (95% CI)	31.8 (25.4, 38.8)	17.4 (12.4, 23.4)	-	2.2 (1.3, 3.6)	0.002†
Clinical Benefit Response Rate (CR or PR or SD $\geq$ 6 months) (%)	36.9	21.4	-	2.1 (1.3, 3.4)	0.001†

* Log-rank two-sided p-value
† Exact test two-sided p-value

Independent vs. Investigator Assessments

As the above tables demonstrate there are differences between the independent- and investigator-assessed data. Such differences between data sets are, for the most part, minor. In an effort to understand these differences, exhaustive analyses on a case-by-case basis was carried out. These differences were ascertained to be the result of variability in the radiological interpretation of progression and response rates by the investigator and independent reviewers, and are balanced across treatment arms. As with any scientific measurement involving human interpretation, differences in the reviewer's observations are to be expected and can lead to differences in the results. The IRC assessed in a blinded fashion without knowledge of the treatment assigned to individual patients, making this assessment more robust and impartial than investigator assessments. Importantly, both investigator and independent assessments confirm the significant clinical benefit seen in the lapatinib plus capecitabine arm. Differences in response rates as assessed by the independent review compared to investigator evaluation have been reported in previous metastatic breast cancer trials (O'Shaughnessy 2002; O'Shaughnessy 2003)

Further analyses of TTP will be conducted once all patients have progressed but, whilst the exact TTP figures may change, it is unlikely that the overall benefit could be lost due to the currently very high statistical difference between treatment groups.

5.4.2.1. Overall survival

There was a 22% reduction in risk of death for patients receiving lapatinib plus capecitabine relative to capecitabine alone at the time of the 03 April 2006 cut-off (Table 5.7, Figure 5.5). The difference in median overall survival is small; however, these data are immature, with 65% of the combination arm and 58% of the capecitabine alone arm still being followed-up and censored for this analysis.

Table 5.7: Summary of overall survival (ITT population, 03 April 2006 cut-off)

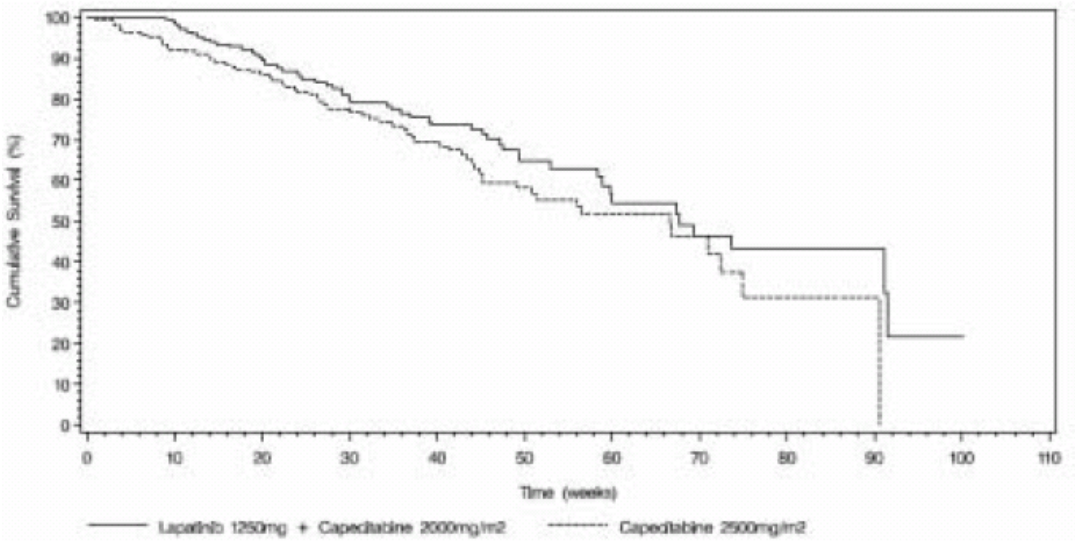
Outcome Measure	Lapatinib + Capecitabine (N=198)	Capecitabine (N=201)	Hazard Ratio (95% CI)	Log-rank 2-sided p-value
Deaths	55 (28%)	64 (32%)	-	-
Censored, follow-up ended Censored, follow-up ongoing	15 (8%) 128 (65%)	20 (10%) 117 (58%)	-	-
Deaths due to disease progression	53 (27%)	59 (29%)	-	-
Median Overall Survival * (weeks) (95% CI)	67.7 (58.9, 91.6)	66.6 (49.1, 75.0)	0.78 (0.55, 1.12)	0.177

* Immature data. Follow-up still ongoing for further survival analyses.

As noted in section 5.3.5.10, it has been recognised that due to the early termination of the trial the detection of a survival difference has been impacted by the lower number of patients enrolled as well as the crossover occurring after the 03 April 2006 halt. Nevertheless, as can be seen in Figure 5.4, the survival effect is present early and persists.

Furthermore, as discussed in section 5.3.4.1, survival in metastatic breast cancer is likely to be extended by as much or more than any incremental delay in tumour progression (RTI Health Solutions report for GSK, data on file). Thus, had the study accrued to its recruitment target and cross-overs not occurred, a statistically significant survival benefit (expected to be at least as great as the TTP advantage) might have been observed with lapatinib plus capecitabine compared with capecitabine alone.

Figure 5.5: Kaplan Meier Estimates of Overall Survival (as assessed by independent review, ITT population, 03 April 2006 cut-off) [Academic in Confidence]



5.4.3. Incidence of brain metastases – post-hoc analysis

The incidence of brain metastases as site of first progression was examined by a post-hoc analysis. Fewer patients in the lapatinib plus capecitabine group had CNS metastases as the first site of relapse than in the capecitabine alone group.

Table 5.8: Summary of CNS metastases as site of first progression (03 April 2006 cut-off)

	Lapatinib + Capecitabine (N=198)	Capecitabine (N=201)	Two-sided p-value
Patients with previously treated and stable brain metastases at baseline (as assessed by independent review)	2	2	-
Patients with CNS metastases as site of first progression	4 (2%)	13 (6%)	0.0445

5.4.4. Response rate by stratification factor

Table 5.9 shows the independently-assessed response rate according to the *a priori* stratification factors. Across all strata, the response rate was superior in the lapatinib plus capecitabine arm than the capecitabine monotherapy arm.

Table 5.9: Response rate by stratification factor (ITT population, 03 April 2006 cut-off)

	Lapatinib + capecitabine (N=198)	Capecitabine alone (N=201)
Overall response rate (CR or PR)	47/198 (24%)	28/201 (14%)
Stage of disease at screening Stage IIIb or IIIc, with T4 lesion Stage IV	 1/7 (14%) 46/191 (24%)	 0/7 (0%) 28/193 (15%)
Site of disease at screening Visceral Non-visceral NA	 37/148 (25%) 9/43 (21%) 1/7 (14%)	 23/158 (15%) 5/35 (14%) 0/8 (0%)
Stage/site of disease Stage IIIb or IIIc with T4 lesion Stage IV - visceral Stage IV – non-visceral	 1/7 (14%) 37/148 (25%) 9/43 (21%)	 0/8 (0%) 23/158 (15%) 5/35 (14%)

5.4.5. Regression analyses

A number of co-variates, which were not pre-specified, and which may be associated with a patient's prognosis, were examined in a proportional hazards model. The only covariate tested that had a significant effect on the independently-assessed TTP was treatment group.

Table 5.10: Summary of Cox proportional hazards regression model for Independently Reviewed TTP (ITT population, 15 November 2005 cut-off)

Co-variate	Effect tested	Hazard ratio (95% CI)	Two-sided p-value
Treatment group	Lapatinib + capecitabine / capecitabine	0.47 (0.32, 0.68)	<0.001
No. of metastatic sites	> 3 sites / < 3 sites	0.98 (0.66, 1.46)	0.931
Stage of disease at screening	Stage IIIb or IIIc with T4 lesion / stage IV	0.86 (0.25, 2.91)	0.806
Stage of disease at screening	Visceral / non-visceral	1.08 (0.68, 1.7	0.744
ER / PR status	ER- PR- / ER+ or PR+	0.60 (0.21, 1.72)	0.345
ER / PR status	Unknown / ER+ or PR+	1.06 (0.72, 1.56)	0.772
Time from last dose of trastuzumab to randomisation	< 8 weeks / > 8 weeks	0.85 (0.58, 1.25)	0.418
Age	Trend per one year increase in age	1.01 (0.99, 1.02)	0.561
ECOG Performance Status	0 / > 1	0.79 (0.53, 1.16)	0.230

Further analyses of the effect of interval between administration of trastuzumab and randomisation to study treatment

Approximately 60% of patients in the study had received their last dose of trastuzumab within the previous 8 weeks. It has been suggested that the activity of lapatinib may have been enhanced by the persistence of trastuzumab in the body due to its long half-life (28.5 days) (Sonpavde 2007). An analysis to determine whether the interval from last dose of trastuzumab to randomization affected the activity of lapatinib was carried out for women in the 15 November 2005 dataset for whom the date of administration of the last dose had been reported. Lapatinib plus capecitabine significantly extended TTP compared with capecitabine alone, in both the subset for whom the time interval was $\leq$ 8 weeks (p=0.0007) and in those for whom it was > 8 weeks (p=0.01). In a letter to The New England Journal of Medicine regarding this issue, the authors conclude that the contribution of residual trastuzumab to the activity of lapatinib was minimal (Geyer 2007).

5.4.6. Efficacy in sub-groups

As the number of patients who were older than 65 years was small, no statistical conclusions can be drawn from this analysis but the data do not appear to indicate a difference between the age groups (< 65 years and > 65 years). Similarly, the majority of patients enrolled in the study were white (about 90% in each treatment group) and therefore no statistical conclusions could be drawn from an analysis by racial group.

5.4.7. Quality of life

Changes from baseline in the FACT-B, FACT-G, TOI, and EQ-5D scores were analysed using parametric analysis of covariance (using baseline as a covariate). Missing post-baseline data were imputed using a last observation carried forward method.

Of those patients who completed baseline questionnaires (171/198 patients in the lapatinib plus capecitabine group, 168/201 patients in the capecitabine group), nearly 50% withdrew from the study (mostly due to disease progression). Since few patients completed questionnaires after week 24, the results reported below relate only to visits up to week 24. In addition, since the objective was to look at changes relative to baseline, they are based only on those subjects who completed a baseline questionnaire. Questionnaires completed at unscheduled visits have been excluded, as have any questionnaire completed post-withdrawal as this was outside the protocol.

The results from the analyses of changes from baseline for FACT-B total scores, FACT-G scores, and TOI scores are summarised in Table 5.11. Overall, the combination treatment had slightly more favourable results than capecitabine alone, but no differences were statistically significant.

Table 5.11; Adjusted* changes from baseline for FACT-B Total Scores, FACT-G Scores, and TOI Scores

	Lapatinib + Capecitabine Adjusted Mean	Capecitabine Adjusted Mean	Treatment Difference Mean (95% CI)	p-value
FACT-B total scores				
Week 6	1.6	0.9	0.7 (-1.4, 2.8)	0.505
Week 12	3.1	1.6	1.5 (-0.7, 3.7)	0.186
Week 18	3.0	0.8	2.2 (-0.1, 4.4)	0.057
Week 24	2.8	1.2	1.7 (-0.6, 3.9)	0.157
FACT-G scores				
Week 6	0.7	-0.2	0.9 (-0.9, 2.7)	0.342
Week 12	1.5	0.3	1.2 (-0.7, 3.0)	0.223
Week 18	1.4	-0.2	1.5 (-0.4, 3.5)	0.115
Week 24	1.4	0.1	1.3 (-0.6, 3.2)	0.187
TOI scores				
Week 6	0.4	0.2	0.2 (-1.4, 1.8)	0.794
Week 12	1.8	0.8	1.0 (-0.7, 2.6)	0.244
Week 18	1.8	0.3	1.5 (-0.1, 3.1)	0.061
Week 24	1.6	0.6	1.0 (-0.6, 2.6)	0.240

*Adjusted for baseline score. FACT-B total score: L+C arm, N = 163, C arm, N = 166; FACT-G score: L+C arm, N = 164, C arm, N = 166; TOI score: L+C arm, N = 164, C arm, N = 165
FACT-B total score is the sum of the five subscale scores.
FACT-G score is the sum of four of the five subscale scores (excluding breast cancer subscale).
Trial Outcome Index (TOI) is the sum of the physical well-being, functional well-being, and breast cancer subscale scores.

Baseline EQ-5D utility, thermometer, and domain scores are summarised in Table 5.12. On average, patients in the two treatment arms had similar baseline and thermometer scores. At baseline, fewer patients in the combination arm reported problems performing usual activities than those in the capecitabine alone arm but combination patients had a higher rate of pain or discomfort.

Table 5.12: Summary of baseline EQ-5D Scores

	Lapatinib + Capecitabine		Capecitabine	
	n	**Mean (SD)**	**n**	**Mean (SD)**
Utility scores (score range -0.594 to 1)	168	0.64 (0.258)	163	0.66 (0.240)
Thermometer scores (score range 0 to 100)	163	65.3 (18.68)	163	67.5 (20.10)
Domain scores		**% with no problem**		**% with no problem**
Mobility	169	61%	166	63%
Self-care	169	79%	165	80%
Usual activities	169	49%	166	39%
Pain or discomfort	169	23%	167	30%
Anxiety and/or depression	170	32%	166	36%

Note: This summary is based on observed data. No imputation was made for missing data.

Table 5.13 presents results from the analyses of changes from baseline for EQ-5D utility and thermometer scores. The combination treatment had slightly more favourable results in overall health status, as measured by thermometer score, than capecitabine alone, but there were no statistically significant differences.

Table 5.13: Adjusted* changes from baseline for EQ-5D utility scores and thermometer scores

	Lapatinib + Capecitabine Adjusted Mean	Capecitabine Adjusted Mean	Treatment Difference Mean (95% CI)	p-value
Utility scores				
Week 6	0.01	-0.02	0.03 (-0.00, 0.07)	0.073
Week 12	0.00	0.01	0.00 (-0.04, 0.03)	0.868
Week 18	0.00	-0.01	0.01 (-0.02, 0.05)	0.400
Week 24	0.00	-0.01	0.01 (-0.03, 0.04)	0.631
Thermometer				
Week 6	0.6	-1.2	1.8 (-0.9, 4.5)	0.186
Week 12	1.5	-0.3	1.8 (-0.8, 4.5)	0.175
Week 18	1.5	0.0	1.5 (-1.1, 4.1)	0.267
Week 24	1.0	0.8	0.3 (-2.5, 3.0)	0.843

*Adjusted for baseline score. Utility score: L+C arm, N = 168, C arm, N = 163; Thermometer score: L+C arm, N = 163, C arm, N = 163

To summarise, there was no detriment to quality of life in patients receiving lapatinib plus capecitabine. Further detail on the quality of life assessments and results can be found in Appendix 9.5.

5.4.8. Exposure to study medication

The mean duration of exposure to study medication was longer in the lapatinib plus capecitabine group than in the capecitabine monotherapy group. This difference in the extent of exposure is likely due to the shorter time to disease progression in the capecitabine group compared to the lapatinib plus capecitabine group resulting in patients withdrawing from treatment.

Table 5.14: Summary of exposure to study medication (Safety Population) (03 April 2006 cut-off)

	Lapatinib plus capecitabine N=198		Capecitabine N=191
Medication	**Lapatinib**	**Capecitabine**	**Capecitabine**
Duration of treatment (weeks)			
n	198	196	191
Mean (SD)	21.6 (18.14)	20.7 (17.35)	15.1 (13.80)
Median	19.0	17.5	9.7
Daily dose, mg or mg/m^2			
n	198	196	191
Mean (SD)	1252.0 (164.77)	1864.0 (292.25)	2273.6 (302.24)
Median	1250.0	2000.0	2413.8

5.4.9. Comparison of results from Geyer paper versus Clinical Study Report

The EGF100151 efficacy data presented in this submission are obtained from the GSK CSR [ZM2006/00137/00] for the 399 patients enrolled as of the 03 April 2006 cut-off. These differ from the data presented in the New England Journal of Medicine publication (Geyer 2006b), which are from an earlier analysis with a cut-off date of 15 November 2005 in 324 patients.

Table 5.15: Comparison of EGF100151 results for 15 Nov 2005 cut-off (Geyer 2006b) versus 03 April 2006 cut-off (by independent review)

		15 Nov 2005 cut-off N=324 (Geyer NEJM 2006)		03 April 2006 cut-off n=399 (GSK Clinical Study Report)	
Primary Endpoint		**Lapatinib + Capecitabine N=163**	**Capecitabine N=161**	**Lapatinib + Capecitabine N=199**	**Capecitabine N=201**
Time to Progression	Median (weeks)	36.7	19.1	27.1	18.6
	HR (95% CI)	0.49 (0.34, 0.71)		0.57 (0.43, 0.77)	
	Two-sided p-value	p=0.00008		p=0.00013	
	One-sided p-value	p=0.00004		p=0.000065	
Secondary Endpoints					
Progression-free Survival	Median (weeks)	36.7	17.9	27.1	17.6
	HR (95% CI)	0.47 (0.33, 0.67)		0.55 (0.41, 0.74)	
	Two-sided p-value	p=0.000023		p=0.000033	
	One-sided p-value	p=0.0000115		p=0.0000165	
Overall Survival	Median (weeks)	58.9	NR	67.7	66.6

	HR (95% CI)	0.92 (0.58, 1.46)		0.78 (0.55, 1.12)	
	Two-sided p-value	0.717		0.177	
Overall response rate (CR + PR)	Response %	22.1	14.3	23.7	13.9
	OR (95% CI)	1.7 (0.9, 3.2)		1.9 (1.1, 3.4)	
	p-value	0.091		0.017	
Clinical benefit rate (CR + PR + SD ≥ 6 months)	Response %	27.0	18.0	29.3	17.4
	OR (95% CI)	1.7 (1.0, 3.0)		2.0 (1.2, 3.3)	
	p-value	0.069		0.008	
Patients with CNS relapse	No. of patients	4	11	4	13
	p-value	0.0688		0.0445	

5.5. Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken.

As only one comparative study involving lapatinib plus capecitabine (Cameron 2006a; Cameron 2006b; Geyer 2006a; Geyer 2006b) was identified in the systematic review, no meta-analysis could be carried out.

5.6. Indirect/mixed treatment comparisons

In circumstances where there are no RCTs that directly compare the technology with the comparators of interest, consideration should be given to using indirect/mixed treatment comparisons.

An indirect estimation of comparative treatment effect may be made where no head-to-head trials exist but where the treatments to be compared have been assessed against a common comparator. Head-to-head data of lapatinib in combination with capecitabine versus capecitabine alone does exist (Study EGF100151 as discussed in section 5.4 above) but no studies of lapatinib plus capecitabine or lapatinib alone versus other comparators were found in the systematic review. In addition, no studies comparing the other relevant interventions in the population in question were identified in the systematic review so mixed treatment comparisons are not possible.

Therefore, the limitations of the data mean that (with the exception of the lapatinib plus capecitabine vs. capecitabine comparison) comparisons using data from single-arm studies will be required.

5.7. Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however findings from non-comparative trials may be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse events not significantly associated with other treatments.

Full safety data for lapatinib in combination with capecitabine are available from study EGF100151 and supportive data for lapatinib monotherapy are available from three non-RCTs in patients who had progressed while receiving trastuzumab-containing regimens (EGF20002, EGF20008 and NCI CTEP6969). The methodology and efficacy findings of these three studies are discussed in section 5.8.

5.7.1. EGF100151

There were 389 patients included in the safety analysis for the 03 April 2006 cut-off with patients in the lapatinib plus capecitabine arm (N=198) being exposed to treatment approximately 6 weeks longer than the capecitabine alone arm (N= 191).

Overall lapatinib plus capecitabine was well tolerated with few patients discontinuing treatment because of adverse events (AEs). In total 97% of patients receiving lapatinib plus capecitabine versus 93% on capecitabine alone experienced an adverse event, of which 87% and 82% respectively were deemed by the investigator to be treatment-

related. The overall pattern of AEs was similar between treatment groups with the six most common AEs being diarrhoea, Palmar-Plantar Erythrodysaesthesia (PPE) syndrome, nausea, fatigue, vomiting and rash (Table 5.16). Most AEs associated with lapatinib plus capecitabine were grade 1 or 2; the incidence of grade 3 and 4 toxicities was low and was similar between the two treatment arms.

Table 5.16: Summary of 6 most common AEs, regardless of relationship to study drug (Safety Population, 03 April 2006 cut-off)

Preferred Term	Lapatinib + capecitabine N=198 n (%)	Capecitabine N=191 n (%)
Diarrhoea[1]	128 (65%)	76 (40%)
PPE syndrome	105 (53%)	97 (51%)
Nausea	87 (44%)	83 (43%)
Fatigue	46 (23%)	47 (25%)
Vomiting	52 (26%)	41 (21%)
Rash[2]	(55 (28%)	26 (14%)

1. Diarrhoea includes incidences of diarrhoea, loose stools and frequent bowel movement
2. Rash includes acne, dermatitis, eczema, erythema, folliculitis, rash, popular rash, pustular rash.

Drug-related diarrhoea and rash were more commonly reported in the lapatinib plus capecitabine arm. Both are known class effects of small molecule tyrosine kinase epidermal growth factor receptor (EGFR) inhibitors (Tarceva SmPC; Iressa US Prescribing Information); diarrhoea is also frequently seen with the fluropyrimidines such as capecitabine (Xeloda SmPC). The difference in incidence between treatment groups was primarily due to an increased incidence of grade 1 severity reports in the combination arm. Most cases of diarrhoea reported were transient in nature and did not result in discontinuation of treatment. Most rash events resolved without treatment and none led to permanent discontinuation of study medication.

The incidence of PPE, a well-recognised side effect of capecitabine (Xeloda SmPC; Walko 2005) presenting as reddening/scaling of the hands and/or feet, was similar between the two groups at each toxicity grade; thus, there was no increase in PPE incidence or severity with the addition of lapatinib to capecitabine (Table 5.17). Most of the events were of grade 1 or 2 severity and resolved while patients were on study. However, median time to onset of PPE (40 vs. 21 days) and median duration of PPE (25.5 vs. 17 days) were both longer in the combination group.

Table 5.17: Incidence of the 6 most common AEs related to study medication, by maximum toxicity grade (Safety Population, 03 April 2006 cut-off)

Adverse event	Number (%) of subjects[1]				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Lapatinib + capecitabine, N=198					
Any event	28 (14%)	78 (39%)	60 (30%)	6 (3%)	172
Diarrhoea[2]	56 (28%)	38 (19%)	23 (12%)	2 (1%)	119
PPE	26 (13%)	52 (26%)	19 (10%)	0	97
Nausea	56 (28%)	23 (12%)	1 (<1%)	0	80
Rash [3]	35 (18%)	11 (6%)	3 (2%)	0	49
Vomiting	30 (15%)	8 (4%)	2 (1%)	0	40
Fatigue	18 (9%)	14 (7%)	4 (2%)	0	30
Capecitabine, N=191					
Any event	24 (13%)	73 (38%)	53 (28%)	6 (3%)	156
Diarrhoea[2]	28 (15%)	26 (14%)	17 (9%)	0	71
PPE	23 (12%)	44 (23%)	26 (14%)	0	93
Nausea	47 (25%)	25 (13%)	2 (1%)	0	74
Rash[3]	16 (8%)	5 (3%)	2 (1%)	0	23
Vomiting	17 (9%)	13 (7%)	3 (2%)	0	33
Fatigue	19 (10%)	15 (8%)	6 (3%)	1 (<1%)	41

1. Subjects who experienced the same event multiple times, but with different toxicities, were only counted once at the maximum toxicity
2. Diarrhoea includes incidences of diarrhoea, loose stools and frequent bowel movement
3. Rash includes acne, dermatitis, eczema, erythema, folliculitis, rash, popular rash, pustular rash.

Note: Details of dose delays / dose reductions employed in order to manage toxicity are provided in the CSR.

Serious AEs
The incidence of serious AEs was similar between the two treatment groups (23-24%) with diarrhoea being the most commonly reported SAE, occurring in 6-7% of patients in both groups. There were no deaths considered related to treatment in the lapatinib plus capecitabine arm.

Discontinuations due to AEs
The proportion of patients with AEs leading to permanent discontinuation of study medication was the same in both treatment groups (14%) (Table 5.18). Diarrhoea led to permanent withdrawal of study medication in only 5% and 3% of subjects in the combination and capecitabine alone arms, respectively. PPE resulted in few subjects in either treatment group permanently discontinuing study medication (3% in both arms). Rash led to study medication being temporarily withdrawn in a small proportion of patients (lapatinib plus capecitabine: 4%; capecitabine 1%) but to no permanent discontinuations.

Table 5.18: Summary of AEs leading to permanent discontinuation of study medication reported by > 1 subject, regardless of relationship (Safety Population, 03 April 2006 cut-off)

Adverse event	Lapatinib + capecitabine N=198 n (%)	Capecitabine N=191 n (%)
Any AE leading to discontinuation	28 (14%)	27 (14%)
Diarrhoea[1]	9 (5%)	5 (3%)
PPE syndrome	5 (3%)	5 (3%)
Nausea	3 (2%)	2 (1%)
Vomiting	2 (1%)	2 (%)
Mucosal inflammation	2 (1%)	1 (<1%)
Neutropenia	2 (1%)	1 (<1%)
Pulmonary embolism	1 (<1%)	2 (1%)
Fatigue	2 (1%)	0
CNS metastases	1 (<1%)	1 (<1%)
Dehydration	1 (<1%)	1 (<1%)
Disease progression	1 (<1%)	1 (<1%)

1. Includes incidence of diarrhoea, loose stools and frequent bowel movements

Cardiac events
Cardiac function was closely monitored during study EGF100151. Only 7 (4%) patients in the lapatinib plus capecitabine arm and 2 (1%) patients in the capecitabine arm experienced a decreased LVEF. Five of the 7 events in the combination group were asymptomatic. None of these events in either group led to study discontinuation. No decline from baseline in mean LVEF was observed in either group through to 6 months.

Interstitial pneumonia/pnemonitis events
Interstitial pneumonitis has been reported with small molecule EGFR inhibitors (Iressa US Prescribing Information). Interstitial pneumonia/pnemonitis events were therefore examined as AEs of special interest in the EGF100151 study. No patients in either the lapatinib plus capecitabine or capecitabine alone groups experienced an interstitial pneumonia or pnemonitis event.

Clinical laboratory evaluations
Haematology and clinical chemistry toxicities were reflective of patients with metastatic breast cancer and treatment with capecitabine and were reported with a similar incidence between treatment groups.

5.7.2. Lapatinib supportive safety evidence base from non-RCTs (lapatinib monotherapy)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.7.3. Review of cardiac events across all lapatinib trials

Across the entire lapatinib clinical trial programme (including the EGF100151 study), approximately 4695 patients are estimated to have received lapatinib as of 09 February 2007. As of this date, 70 (1.5%) patients known to have received lapatinib have experienced a decreased LVEF*. Ten patients (0.2%) had a symptomatic LVEF decrease* (dyspnoea, palpitations, symptoms of congestive heart failure).

The mean LVEF decrease relative to baseline across all 70 patients was 30% (range: 20-66%). The mean time to onset of LVEF decrease was 12 weeks (range: 2 weeks to 1 year). The majority of patients with decreased LVEF had confounding factors that may have contributed to the event, including mediastinal or left-sided radiation therapy, and /or medical history (e.g. myocardial infarction, underlying congestive heart failure, coronary artery disease, hypertension, diabetes). Additionally, the incidence of LVEF decrease was similar between patients with prior exposure to anthracyclines or trastuzumab versus those with no prior exposure to these agents.

Overall, 6 of the 10 symptomatic patients recovered following treatment with standard therapies such as nitroglycerin and diuretics. Three subjects died due to progressive disease whilst the event was ongoing. The remaining symptomatic patient developed cardiac failure and died. This patient was receiving lapatinib in combination with trastuzumab and had a history of hypertension. The investigator commented that the most probable cause of death was pulmonary thromboembolism. Forty two of the 64 asymptomatic patients recovered or improved, 18 of these while continuing to receive lapatinib. Ten asymptomatic events were ongoing at the time of the patient's death due to disease progression, 3 patients were lost to follow-up and 5 events were ongoing at the time of reporting.

In conclusion, LVEF decreases associated with lapatinib therapy are infrequent, generally asymptomatic, reversible and non-progressive.

* Cardiac event defined as

Symptomatic (NCI CTCAE grade 3 or 4)
or
Asymptomatic ↓ LVEF (≥ 20% relative to baseline *and* below the institution's lower limit of normal (LLN)

5.7.4. Lapatinib safety conclusions

Lapatinib in combination with capecitabine is well tolerated in advanced / metastatic breast cancer. The combination is associated with a similar pattern of AEs as would be seen with each single agent. AEs observed with lapatinib in combination or as monotherapy were generally mild to moderate, and transient in nature. Diarrhoea and rash were more common with lapatinib in combination with capecitabine than with capecitabine alone, but this was primarily accounted for by an increase in grade 1 events with combination therapy. The cardiac safety experience for lapatinib to date shows a very low number of cases of decreased LVEF, which are largely asymptomatic and reversible (Perez 2006). The proposed SmPC recommends that LVEF is evaluated prior to and during treatment with lapatinib. This is consistent with the cardiac monitoring used during the lapatinib clinical trials, and similar to the requirements for some other breast cancer agents (e.g. anthracyclines or trastuzumab).

5.7.5. Comparator safety evidence base from non-RCTs

5.7.5.1. Trastuzumab combination therapy

Five prospective (Tripathy 2004; Bangemann 2000; Suzuki 2003; Extra 2006; Bartsch 2006) and seven retrospective (Montemurro 2006; Fountzilas 2003; Gelmon 2004; Stemmler 2005; Tokajuk 2006; Garcia-Saenz 2005; Shmeuli 2004) studies were identified examining continued trastuzumab therapy in patients that had progressed following initial trastuzumab therapy (see section 5.8).

Safety data in these studies is poorly reported, with many studies not fully reporting all AEs. A number of studies reported trastuzumab-related AEs only. In most studies the incidence of trastuzumab-related AEs was limited to mild or moderate events. Neutropenia, anaemia and fatigue were most commonly reported (Table 5.20), along with cardiac dysfunction which is described separately (Table 5.21).

Cardiac dysfunction

The H0659g study (Tripathy 2004) reported a total of 16 patients that experienced at least one cardiac dysfunction event, half of which were symptomatic (NYHA class III or IV). Only 2 of these patients had previously been treated with trastuzumab (2% of the whole trastuzumab pre-treated population) while 14 patients were trastuzumab-naïve (9% of the trastuzumab-naïve population). Ten of the 19 reports of patients experiencing a serious adverse event (SAE) possibly related to trastuzumab therapy were for cardiac dysfunction, irrespective of prior trastuzumab therapy.

In the study reported by Gelmon et al, of the 22 patients that experienced a cardiac event, trastuzumab was continued in 10 patients, with 18 of the 22 patients receiving at least another line of trastuzumab therapy (Gelmon 2004). In patients where trastuzumab was continued only two reported another cardiac event. One of these patients experienced a decrease in LVEF. The other patient developed clinical cardiac failure and trastuzumab was discontinued at this point.

Table 5.20: Severe adverse events reported for patients treated with trastuzumab beyond disease progression (n, (%))

Study	Treatment	All serious AEs	Nausea/ vomiting	Haematological events	Stomatitis	Diarrhoea	Hand-foot syndrome (PPE)	Head-ache	Pain	Fatigue / Asthenia	Infection	Peripheral neuro-pathy	Consti-pation	Oedema
Prospective														
H0659g Tripathy 2004	trastuzumab ± chemotherapy (N = 93)	44 (47%)		Leucopenia 11%				6%	Pain 10% Back pain 6%	10%				
Suzuki 2003*	vinorelbine + trastuzumab (N=24)	3 (12.5%)		Neutropenia 3 (12.5%)										
Bartsch 2006**	trastuzumab + chemotherapy (N = 54)	33 (61%)	1 (2%)	Neutropenia 19 (35%) Anaemia 6 (11%) Thrombocytopenia 2 (4%)	2 (4%)	0	3 (6%)							
Prospective														
Fountzilas 2003	trastuzumab ± chemotherapy (N = 80)		6%	Neutropenia 25% Thrombocytopenia 11.5%	6%	6%				12.5%	10%	9%	6%	6%

Note:
AEs were not reported except cardiotoxicity (see Table 5.21) in the following studies: Bangemann 2000, Gelmon 2004
No AEs were reported in the following studies: HERMINE (Extra 2006), García-Sáenz 2005, Montemurro 2006, Stemmler 2005, Tokajuk 2006, Shmeuli 2004
* based on NCI-CTC grade 3
** based on WHO grade III and IV

Table 5.21: Cardiac events reported for patients treated with trastuzumab beyond disease progression

Study	Treatment	All cardiac events	Serious cardiac event
Prospective			
H0659g§ Tripathy 2004	trastuzumab ± chemotherapy (N = 93)	2 (2%)	1 (1%)
Bangemann 2000‡	trastuzumab + chemotherapy (N=90) trastuzumab + vinorelbine (N = 10) trastuzumab + capecitabine (N = 17) trastuzumab + docetaxel (N = 9)	2/117*	NR
Suzuki 2003	vinorelbine ± trastuzumab (N=24)	0	NR
Bartsch 2006	trastuzumab + chemotherapy (N = 54)	1	0
Retrospective studies			
Fountzilas 2003	trastuzumab ± chemotherapy (N = 80)	NR	1
Gelmon 2004	trastuzumab monotherapy (N = 11) trastuzumab + paclitaxel (N = 21) trastuzumab + vinorelbine (N = 33)	22/105†	NR
Stemmler 2005	trastuzumab ± chemotherapy (N = 23)	NR	0[#]
*number of events per number of therapies; some patients were trastuzumab-naïve § cardiac event reported as cardiac dysfunction ‡reported as cardiac side effect †cardiac event reported for all patients including those receiving trastuzumab as first-line therapy [#] treatment related No AEs were reported in the following studies: HERMINE (Extra 2006), García-Sáenz 2005, Montemurro 2006, Tokajuk 2006, Shmeuli 2004			

Supportive information on adverse events associated with trastuzumab can be found in the Herceptin SmPC. Adverse reactions reported in at least 10% of patients, and between 1 and 10% of patients, in two pivotal clinical trials in first-line metastatic breast cancer are presented below (Herceptin SmPC):

Table 5.22: Adverse events in trastuzumab pivotal trials in first-line metastatic breast cancer (Herceptin SmPC)

Event	> 10%	> 1% and < 10%
Body as a whole	abdominal pain, asthenia, chest pain, chills, fever, headache, pain	flu-like illness, back pain, infection, neck pain, malaiase, hypersensitivity reaction, mastitis, weight loss
Cardiovascular	-	vasodilation, supraventricular tachyarrhythmia, hypotension, heart failure, cardiomyopathy, palpitation
Digestive	diarrhoea, nausea, vomiting	anorexia, constipation, dyspepsia, liver tenderness, dry mouth, haemorrhoids
Blood and lymphatic	-	leucopenia, ecchymosis
Metabolic	-	peripheral oedema, oedema
Musculoskeletal	arthralgia, myalgia	bone pain, leg cramps, arthritis
Nervous	-	dizziness, paraesthesia, somnolence, hypertonia, peripheral, neuropathy, tremor
Psychiatric disorders	-	anxiety, depression, insomnia
Respiratory	-	asthma, cough increased, dyspnoea, epistaxis, lung disorders, pharyngitis, rhinitis, sinusitis
Urogenital	-	urinary tract infection
Skin and appendages	rash	pruritus, sweating, nail disorder, dry skin, alopecia, acne, maculopapular
Special senses	-	taste perversion

Cardiotoxicity

Reduced ejection fraction and signs and symptoms of heart failure, such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, and S_3 gallop, have been observed in patients treated with trastuzumab, either alone or in combination with a taxane, particularly after anthracycline therapy (Herceptin SmPC). The incidence of cardiac events from a retrospective analysis of data from a study of trastuzumab monotherapy in first-line metastatic breast cancer are shown below.

Table 5.23: Cardiac adverse event incidence with trastuzumab monotherapy in first-line metastatic breast cancer (Herceptin SmPC)

	Trastuzumab monotherapy N=213
Symptomatic heart failure	18 (8.5%) (5.1, 13.0)
Cardiac diagnosis other than heart failure	7 (3.3%) (1.3, 6.7)

Note: There are restrictions regarding the use of trastuzumab in patients with an LVEF of 55% or less or with other cardiac conditions. However, these restrictions relate to the use of trastuzumab in the adjuvant rather than the metastatic setting (Herceptin SmPC; NICE TA. No 107).

5.7.5.2. Capecitabine monotherapy

A summary of the safety data reported for the mixed HER2+ and HER2- population receiving capecitabine monotherapy in the Miller study (Miller 2005) is presented below. Although the incidence of cardiac events was low (2/215 patients), they were grade 4 in severity. One patient experienced congestive heart failure and one patient experienced cardiomyopathy.

Table 5.24: Summary of safety data for capecitabine monotherapy arm (Miller 2005)

Toxicity	**Grade 2**	**Grade 3/4**
Diarrhoea*	34 (16%)	23 (11%)
Stomatitis	11 (5.1%)	1 (0.5%)
Hand-foot syndrome*	77 (36%)	52 (24%)
Anaemia	8 (4%)	1 (1%)
Nausea	30 (14%)	4 (2%)
Asthenia	35 (16.3%)	14 (6.6%)
Headache	9 (4%)	1 (1%)
Pain	20 (9%)	4 (2%)
Cardiac events†	0 (0%)	2 (1%)

*common capecitabine toxicities; † includes congestive heart failure and cardiomyopathy

Further information on adverse events associated with capecitabine can be found in the Xeloda SmPC. This supports the findings in the Miller study, with the most commonly reported treatment-related events listed on the SmPC being gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain, stomatits), fatigue and PPE (hand-foot) syndrome. Laboratory abnormalities include thrombocytopenia, leucopenia, neutropenia, anaemia, and hyperbilirubaemia (Xeloda SmPC).

5.7.5.3. Vinorelbine monotherapy

No studies investigating vinorelbine monotherapy in HER2+ patients previously treated with trastuzumab were identified, and hence, safety data are drawn from the Navelbine SmPC. The most commonly reported treatment-related events are gastrointestinal (mainly diarrhoea, nausea, vomiting), neurological (peripheral neuropathy) and haematological (neutropenia, anaemia, thrombocytopenia). Other undesirable events include injection site reactions, alopecia and occasional jaw pain.

The main limiting toxicity is neutropenia which is reversible (peaks at 5 to 7 days) and non-cumulative (Navelbine SmPC).

Table 5.25: Undesirable effects associated with vinorelbine (Navelbine SmPC)

Event	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	9.7%	15.2%	24.3%	27.8%
Anaemia	61.2%.		7.4%	
Thrombocytopenia	5.1%		2.5%	
Peripheral neurpathy	17.2%	3.6%	2.6%	0.1%
Autonomic neuropathy	16.%	4.9%	2%	0.7%
Diarrhoea	7.6%	3.6%	0.7%	0.1%
Nausea & vomiting	19.9%	8.3%	1.9%	0.3%
Injection site pain/local phlebitis	12.3%	8.2%	3.6%	0.1%
Alopecia	21%		4.1%	

5.8. Non-RCT evidence

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The level of detail provided should be the same as for the RCTs and where possible more than one independent source of data should be examined to explore the validity of any conclusions. Inferences about relative treatment effects drawn from observation evidence will necessarily be more circumspect than those from RCTs.

Three, non-comparative, phase II trials of lapatinib (Table 5.26) and a further 12 studies (including one case series) which did not include lapatinib but involved relevant comparators*, met the inclusion criteria for the systematic review. The capecitabine monotherapy arm of Miller et al, an RCT, is also described in this section.

* The comparators were:

- Lapatinib regimens
- Capecitabine monotherapy
- Vinorelbine monotherapy
- Trastuzumab monotherapy
- Trastuzumab plus capecitabine
- Trastuzumab plus vinorelbine
- Trastuzumab plus non-specified or mixed single-agent chemotherapy

The design, methodology and results of these studies will be presented in this section. Their findings will be discussed further in the interpretation of clinical evidence (section 5.9) in order to provide some contextual understanding of the effectiveness and tolerability of lapatinib in this relapsed, advanced disease setting.

The following tables (5.26 and 5.27) list the lapatinib and non-lapatinib non-RCTs identified.

Table 5.26: Relevant non-randomised studies, which included lapatinib meeting the inclusion criteria for the systematic review.

Study	Study Design	Country/Centre status	Intervention	ITT population N	Participants	Prior therapy		HER2 positive population	Main objective
EGF 20002 Data from CSR (Abstracts: Kaplan 2003; Blackwell 2004a; Blackwell 2004b; Blackwell 2005)	Phase II, open-label	Multicentre • US	Lapatinib 1250mg (n = 34) Lapatinib 1500mg (n = 44)	78	Patients with HER2+ stage IIIB or IV breast cancer and who had experienced disease progression whilst treated with trastuzumab.	Any chemotherapy for advanced/metastatic disease =100% Anthracycline = 59% Taxane = NR Taxane & anthracycline = NR Advanced/ metastatic trastuzumab = 100% • 1st line = 79% • 2nd line = 46% • 3rd line = 12%		100%*	To evaluate tumour response rate (CR or PR) in patients with advanced or metastatic breast cancer treated with lapatinib who had progressed while receiving trastuzumab-based regimens.
EGF 20008 Data from CSR (Abstracts: Burstein 2004; Blackwell 2005)	Phase II, open-label	Multicentre • US • Germany • Belgium • UK • France • Spain • Canada • Japan • Australia • Argentina	Lapatinib 1500mg	229 Cohort A n =140 Cohort B n = 89	Patients with advanced or metastatic breast cancer and who had experienced disease progression on prior treatment with regimens containing anthracyclines, taxanes and capecitabine. Patients in Cohort A were HER2+ and had also received prior trastuzumab.	<u>Cohort A</u> Anthracycline > 99% Taxane > 99% Anthracycline & Taxane = NR Advanced /metastatic trastuzumab = 100%	<u>Cohort B</u> Anthracycline > 99% Taxane > 99% Anthracycline & Taxane = NR Advanced / metastatic Trastuzumab = 2 (2%)	Cohort A & B combined = 61% Cohort A = 100% Cohort B = 0%	To evaluate tumour response rate (CR or PR) in two cohorts of advanced or metastatic breast cancer patients treated with lapatinib. Cohort A: Subjects with HER2+ tumours who were refractory to taxane-, anthracycline-, capecitabine- and trastuzumab- containing regimens. Cohort B: Subjects with HER2- tumours and who were refractory to taxane-, anthracycline-, and capecitabine- containing regimens.
CTEP 6969 Data from abstracts (Abstracts: Lin 2006; Van den Abbeele 2006) Investigator-initiated trial not GSK sponsored	Phase II, open label	Single centre • US	Lapatinib 1500mg	39	Patients with HER2+ breast cancer with new or progressive brain metastases and at least one measurable lesion (LD≥1cm). All patients had received prior trastuzumab. Patients were eligible if they had progressed after radiation therapy.	Anthracycline n = 26 (67%) Taxane n = 35 (90%) Taxane & anthracycline = NR Advanced/metastatic trastuzumab n = 39 (100%) • 1st line n = 14 (36%) • 2nd line n = 14 (36%) • 3rd line n = 11(28%)		100%*	To evaluate the clinical efficacy and safety of lapatinib in patients with CNS metastases from HER2+ breast cancer.

* inferred value

Table 5.27: relevant non-randomised studies meeting the inclusion criteria for the systematic review and including potentially relevant interventions other than lapatinib

Study	Study design	Country/centre status	Intervention	ITT population N (n[$])	Participants	Prior therapy (subgroup)	HER2 positive population	Main study objectives / study description
Prospective Studies								
Miller 2005	Phase III, Randomised controlled trial	Multicentre US	Arm A: capecitabine 2500 mg/m^2/d d1-14 q21d	230	Patients with metastatic breast cancer previously treated with anthracyclines and taxanes. HER2+ patients had been previously treated with trastuzumab.	anthracycline = NR taxane = NR taxane & anthracycline = NR trastuzumab = 20.4%*	Arm A: 20.4%	To compare the efficacy and safety of capecitabine with or without bevacizumab in patients with metastatic breast cancer previously treated with an anthracycline and a taxane.
H0659g Tripathy 2004 (Tripathy 2000)	Trial extension study of prospective studies of trastuzumab in HER2+ patients	Multicentre • Canada • Germany • UK • US • Australia • New Zealand • Switzerland • Austria • France	trastuzumab 2mg/kg/w with or without chemotherapy	247 (93)	Patients with HER2+ metastatic breast cancer. Prior treatment included anthracyclines, and/or taxanes and trastuzumab.	anthracycline = 100%* (100%*) taxane = 47% (46%) trastuzumab = 37.7% (100%) anthracycline & taxane & trastuzumab = 17.4%* (46%*)	100%	To obtain additional safety information for trastuzumab in combination with chemotherapy following documented disease progression. Prior therapy included chemotherapy with and without trastuzumab.
Bangemann 2000 (Conference abstract)	Trial extension of prospective studies of trastuzumab in HER2+ patients	Single-centre • Germany	trastuzumab 2mg/kg/w with mixed chemotherapy (vinorelbine 25mg/m^2 weekly or capecitabine 2000mg/m^2 on d1-14 q3w or docetaxel 75mg/m^2, q3w)	90 (36)	Patients with HER2+ metastatic breast cancer. Prior treatment included anthracyclines and/or taxanes.	anthracycline = NR taxane = NR taxane and/or anthracycline = 79%[+] trastuzumab = 100%	100%	To evaluate trastuzumab in combination with vinorelbine, capecitabine, and docetaxel. This sequential study concentrates on the population of patients who progressed from the first regimen (weekly trastuzumab, either with no chemotherapy or weekly paclitaxel). The patients who progressed were further treated with vinorelbine (n=10), capecitabine (n=17) and docetaxel (n=9).
Suzuki 2003	Phase II, non-comparative, single-centre study	Single centre • Japan	vinorelbine 25mg/m2 qw +trastuzumab 2mg/kg qw	24	Patients with HER2+ metastatic breast cancer that had not responded to or had relapsed after treatment with trastuzumab or a combination of trastuzumab and a taxane. Patients had been previously treated with one or two lines of chemotherapy in the metastatic setting.	anthracycline = NR taxane = 79% taxane & anthracycline = NR trastuzumab = 100%	100%	To determine the response rate and toxicity of vinorelbine/trastuzumab as second or third line therapy for metastatic breast cancer in patients whose tumours did not respond to or relapsed after initial trastuzumab therapy.

Study	Study design	Country/centre status	Intervention	ITT population N (n[$])	Participants	Prior therapy (subgroup)	HER2 positive population	Main study objectives / study description
Bartsch 2006	Prospective observational study	Single centre • Austria	trastuzumab 6mg/kg q3w + chemotherapy	54	Patients had histologically confirmed HER2+ advanced breast cancer. Trastuzumab was administered as first-line therapy in all patients except 14 who had prior treatment with aromatase inhibitors. All patients had received at least two lines of palliative trastuzumab treatment.	anthracycline = 35%[+] taxane = 24%[+] taxane & anthracycline = NR trastuzumab = 100%	100%	The objective of this study was to examine continued trastuzumab treatment beyond disease progression.
HERMINE (Conference abstract, Extra 2006)	Prospective observational study[*]	Multicentre • France	trastuzumab dose unspecified ± chemotherapy	177 (107)	Women with metastatic breast cancer who had begun trastuzumab treatment for the first time between Jan and Dec 2002 were eligible. 79% of patients had previously been treated with chemotherapy in the adjuvant/ neoadjuvant setting, with 88% of patients having received anthracycline treatment.	anthracycline = 76% (88%) taxane = NR taxane & anthracycline = NR trastuzumab = 100%*	96% (of 169)	To determine whether continuation of trastuzumab treatment after progression was beneficial.
Retrospective studies								
Fountzilas 2003	Retrospective study	Multicentre • Greece	trastuzumab ± chemotherapy	80	Patients had HER2+ metastatic breast cancer previously treated with trastuzumab and chemotherapy that was treated with further trastuzumab upon progression.	anthracycline = 33% adjuvant anthracycline = 35% taxane = 41% adjuvant taxane = 6% trastuzumab = 100%*	100%	Retrospectively reviewed the medical records of patients who received trastuzumab monotherapy or combination chemotherapy beyond disease progression in order to register their clinical course.
García-Sáenz 2005 (García-Sáenz 2004)	Retrospective study	Single centre • Spain	trastuzumab 2 mg/kg qw ± chemotherapy	58 (31)	Patients had HER2+ (IHC3+) metastatic breast cancer treated with at least 1 trastuzumab containing regimen for metastatic disease. 31 patients received a second line of trastuzumab therapy.	anthracycline = NR adjuvant anthracycline = 44% taxane = NR adjuvant taxane = 16% taxane & anthracycline = NR trastuzumab = NR	100%	To determine the activity of successive trastuzumab-containing regimens in HER2-overexpressing metastatic breast cancer.
Gelmon 2004	Retrospective study	Multicentre • Canada • Europe • Australia	trastuzumab ± chemotherapy	105 (65**)	Patients had HER2+ metastatic breast cancer treated with at least 2 lines of trastuzumab-containing therapy.	anthracycline = 39% adjuvant anthracycline = 51% taxane = 48% adjuvant taxane = 4% taxane & anthracycline = NR trastuzumab = 100%*	97%	To evaluate whether there was any evidence of efficacy to support continuation of trastuzumab beyond disease progression and evaluate the feasibility of this approach.
Montemurro 2006	Retrospective study	Multicentre • Italy	trastuzumab ± chemotherapy (or endocrine	184 (40)	Patients had HER2+ advanced breast cancer treated with trastuzumab. 40 patients continued	anthracycline = 70% taxane = 36% taxane & anthracycline =	100%	To describe patterns of treatment and clinical outcome in patients with HER2-positive

Study	Study design	Country/centre status	Intervention	ITT population N (n[$])	Participants	Prior therapy (subgroup)	HER2 positive population	Main study objectives / study description
			therapy)		trastuzumab treatment after progression on a trastuzumab-containing therapy.	NR trastuzumab=100%*		advanced breast cancer progressing on trastuzumab-based therapy.
Shmueli 2004	Retrospective case series	Single centre • Israel	trastuzumab ± chemotherapy	41 (5)	Patients with HER2+ metastatic breast cancer treated with trastuzumab. 10 patients who developed CNS metastases while on trastuzumab therapy were continued on trastuuzmab (either alone or in combination with chemotherapy).	anthracycline = NR taxane = NR taxane & anthracycline = NR trastuzumab = 100%*	100%*	To describe a series of patients treated with trastuzumab at a single centre, in particular 10 patients who developed CNS metastases after an initial response.
Stemmler 2005	Retrospective study	Multicentre • Germany	trastuzumab 2mg/kg qw ± chemotherapy	136 (23)	Patients with HER2+ (IHC3+) metastatic breast cancer treated with trastuzumab. 23 patients received trastuzumab after progressing on a trastuzumab containing regimen.	anthracycline = NR adjuvant anthracyclines 41.2% taxane = NR adjuvant taxanes 19.9% taxane & anthracycline = NR trastuzumab = 100%*	100%	To evaluate the impact of trastuzumab-based regimens on the survival of patients with HER2-overexpressing metastatic breast cancer.
Tokajuk 2006	Retrospective study	Single centre (country not reported)	trastuzumab (standard doses) ± chemotherapy	27 (14)	Patients with HER2+ metastatic breast cancer, heavily pre-treated	anthracycline = NR adjuvant anthracyclines NR taxane = NR adjuvant taxanes = NR taxane & anthracycline = NR trastuzumab = 100%	100%	To assess the activity of trastuzumab-based therapy for metastatic breast cancer patients treated in a single institution outside clinical trials.

* inferred value

+ baseline value

** Second line of trastuzumab used in 93 patients but response rates reported for 65 patients

[$] n = patients treated after progression on trastuzumab. Results for these studies in Table 5.36 are reported for these subgroups.

NR = Not recorded

NA = Not applicable

5.8.1. Summary of methodology of relevant non-RCTs

5.8.1.1. Lapatinib

Three non-comparative, phase II trials of lapatinib were identified in the review. It is important to note that these are supportive studies involving lapatinib monotherapy rather than lapatinib plus capecitabine, the technology under consideration. The study methods and objectives are summarised in Table 5.26 above.

Main inclusion and exclusion criteria

Table 5.28: Main inclusion and exclusion criteria for lapatinib non-RCTs

Study	Inclusion	Exclusion
EGF20002	• Females aged ≥ 18 years with life expectancy ≥ 12 weeks • Histologically or cytologically confirmed stage IIIb or IV breast cancer • HER2 overexpression (defined as IHC2+ or 3+ and FISH+) • Patients must have progressed while receiving at least 6 weeks (≤ 2 regimens) of trastuzumab for metastatic disease • Measurable disease according to RECIST criteria • At least an 8-week period between last radiotherapy and screening • Discontinued trastuzumab ≥ 2 weeks and/or discontinued other therapies (except for minor surgical procedures) prior to treatment with study medication • Karnofsky Performance Score (KPS)* > 70 • Cardiac ejection fraction within institutional range of normal as measured by ECHO or MUGA scan	• Known history of severe cardiovascular disease or cardiac disease requiring a device • Prior therapy with EGFR or HER2 inhibitor other than trastuzumab • Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery immunotherapy, biologic therapy, hormonal therapy) or steroid use (oral or intravenous)
EGF20008	• Females aged ≥ 18 years with life expectancy ≥ 12 weeks • Histologically or cytologically confirmed stage IIIb or IV breast cancer • Refractory breast cancer, defined as progression after prior therapy including: o at least four cycles of anthracycline- and taxane-containing regimens, or o at least two cycles, provided disease progression occurred while receiving the respective anthracycline- or taxane-containing chemotherapy regimen(s) o prior treatment for ≥ 6 weeks with capecitabine o for Cohort A subjects, prior treatment had to contain trastuzumab alone or in combination with other chemotherapy for ≥ 6 weekly doses • Subjects eligible for Cohort A had HER2 overexpression (defined as IHC2+, IHC3+ and FISH+) • Measurable disease according to RECIST criteria • At least a 3-week period between last radiotherapy and other therapies (a 2-week period after trastuzumab) before starting lapatinib therapy • Subjects with stable CNS metastases were eligible • ECOG PS 0-2* • Cardiac ejection fraction within institutional range of normal as measured by ECHO (or MUGA scan)	• Known history of uncontrolled or symptomatic angina, arrythmias or congestive heart failure • Prior therapy with EGFR or HER2 inhibitor other than trastuzumab • Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery immunotherapy, biologic therapy, hormonal therapy)
NCI CTEP6969	• Metastatic HER2+ breast cancer • New or progressive CNS metastases after WBRT and/or SRS *or* Asymptomatic CNS metastases w/o prior radiation therapy • ECOG PS 0-2* • At least one CNS lesion ≥ 10 mm in longest dimension	• Cardiac ejection fraction below institutional normal limit • Prior treatment with EGFR or HER2 inhibitor, other than trastuzumab, for MBC • Concurrent treatment with inducers or inhibitors of CYP3A4
*ECOG PS 0 = fully active, able to carry on all pre-disease performance without restriction) 1 = restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature) 2 = ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours		

*KPS
100 = normal; no complaints; no evidence of disease
90 = able to carry on normal activity; minor signs or symptoms of disease
80 = normal activity with effort; some signs or symptoms of disease
70 = cares for self; unable to carry on normal activity or do active work

WBRT = whole brain radiation therapy; SRS = stereotactic radiosurgery

Baseline characteristics

Table 5.29: Baseline characteristics for lapatinib non-RCTs

Study	Characteristic	Population	
EGF20002 N=78	Age (median, years) KPS ≥ 90 ER- / PR- Stage IV disease ≥ 2 metastatic sites	54.5 64 (83%) 35 (45%) 77 (99%) 59 (76%)	
EGF20008 N=229		Cohort A N=140	Cohort B N=89
	Age (median, years) ECOG PS ≤ 1 ER- / PR- Stage IV disease ≥ 2 metastatic sites	52.0 119 (88%) 68 (49%) 129 (92%) 122 (88%)	54 69 (80%) 27 (30%) 88 (99%) 84 (94%)
NCI CTEP 6969 N=39	Age (median, years) ECOG PS ≤ 1 ER- / PR- Median no. metastatic sites CNS metastases	52 31 (79%) 17 (44%) 3 100%	

Efficacy endpoints

Table 5.30: Study endpoints in lapatinib non-RCTs

Study	Outcome Measures
EGF20002	Primary: • Overall response rate (CR or PR) Secondary: • Clinical benefit rate (CR or PR or SD ≥ 6 months) • Time to response • Duration of response • TTP • 4- and 6- months PFS • Toxicity • Tissue/serum biomarker expression
EGF20008	Primary: • Overall response rate (CR or PR) Secondary: • Clinical benefit rate (CR or PR or SD ≥ 6 months) • Time to response • Duration of response • TTP • 4- and 6- months PFS • Overall survival • Toxicity • Tissue/serum biomarker expression • Quality of life
NCI CTEP6969	Primary: • Objective response rate in the CNS Secondary: • Objective response rate in non-CNS sites • TTP • Overall survival • Toxicity • Quality of life

Statistical analysis and definition of study groups

Table 5.31 presents details of the hypotheses under consideration, sample size and analyses plans for the lapatinib non-RCTs. A full description of the statistical plans for studies EGF20002 and EGF20008 can be found in the relevant CSRs.

Table 5.31: Sample size considerations for lapatinib non-RCTs

Study	Sample size, hypothesis and data analyses
EGF20002	• Two-stage design with stopping rule. 40 subjects were to be recruited in stage I. If there was zero or one responder, this would support the null hypothesis and the study would be terminated. Otherwise, the study would progress to stage II and a further 40 subjects would be accrued. If there were $\leq$ 7 responders among all 80 recruited subjects, then this would support the null hypothesis. If there were $\geq$ 8 responders, then data would support the alternative hypothesis. • The ITT population (defined as all subjects who received at least one dose of study medication) was used to analyse efficacy and safety data.
EGF20008	• Two-stage design allowing study enrolment to be terminated at end of stage I if strong evidence of lack of efficacy (i.e. disease progression) based on independently assessed tumour response rate in first 40 subjects in each cohort followed for at least 16 weeks. Otherwise study would progress to stage II and a further 80 subjects would be recruited for Cohort A and a further 40 for Cohort B. Stage II ended when all subjects had been followed for 16 weeks (or until death, progression or withdrawal if sooner). • Cohort A: If there were $\leq$ 11 responders among all 120 subjects, this would support the null hypothesis (H_0: p=5%). If there were $\geq$ 12 or more respondents, the data would support the alternative hypothesis (H_A: p=15%). Cohort B: If there were $\leq$ 7 responders among all 80 subjects, this would support the null hypothesis (H_0: p=5%). If there were $\geq$ 8 or more respondents, the data would support the alternative hypothesis (H_A: p=15%). For all analyses, Cohorts A and B were analysed independently. • The ITT population (defined as all subjects who received at least one dose of study medication) was used to analyse efficacy and safety data. Endpoints were analysed by independent-review and investigator-review.
NCI CTEP6969	• Two-stage accrual design. The accrual goal was 37 patients (n=12 first stage; n=25 second stage) with $\geq$ 1 response seen in first 12 patients to proceed to full accrual. Otherwise accrual would terminate. • H_0 – RR $\leq$ 5%. H_A – RR $\geq$ 20%. At least 4 responses were required to reject the null hypothesis. The trial had a 90% chance of positive findings if the true response rate was 20% and a 10% chance of positive findings if the true response rate was 5%.

5.8.1.2. Trastuzumab-containing therapy

Five prospective studies (Tripathy 2004; Bangemann 2000; Suzuki 2003; Extra 2006; Bartsch 2006) and seven retrospective studies (Monetmurro 2006; Fountzilas 2003; Gelmon 2004; Stemmler 2005; Tokajuk 2006; García-Sáenz 2005; Shmueli 2004) investigated continued treatment with trastuzumab after progression on trastuzumab in the metastatic setting. The individual study designs are summarised in Table 5.27.

Prospective studies

Two of the prospective studies (Bangemann 2000; Tripathy 2004) were trial extensions of prospective studies of trastuzumab in patients with HER2+ metastaic breast cancer. A third, small study reported by Suzuki evaluated trastuzumab in combination with vinorelbine in patients who had progressed or not responded to a trastuzumab-based regimen (Suzuki 2003). Two prospective observational studies (Extra 2006 [HERMINE]; Bartsch 2006) also evaluated the continuation of trastuzumab beyond progression.

Retrospective studies

The seven retrospective studies included patients with HER2+ metastatic breast cancer, some or all of whom received trastuzumab beyond disease progression. In all of these studies trastuzumab was administered either alone or in combination with different chemotherapy regimens.

Montemurro et al reviewed the outcomes for patients receiving a second trastuzumab-based regimen after progression on initial trastuzumab therapy (Montemurro 2006). Two other studies, Fountzilas et al and Gelmon et al, specifically reviewed patients who had progressed on trastuzumab-based therapy and received a further line(s) of trastuzumab (Fountzilas 2003; Gelmon 2004). The three remaining retrospective studies reviewed patients who had received trastuzumab-based therapy for metastatic breast cancer, and included subgroups that received further trastuzumab-containing therapy (Stemmler 2005; Tokajuk 2006; García-Sáenz

2005). A case series reported by Shmueli et al was also identified (Shmueli 2004). This study is not described further as it does not provide data to contribute to the decision problem.

Three protocols for studies involving the continuation of trastuzumab beyond disease progression were also found ((i) NCT00148876 [German Breast Group study 26]; (ii) Pusztai 2005 [SWOG S0347, NCT00103233]; (iii) NCT00130507), but no data have been reported from these and they are not discussed further. The SWOG S0347 study is now closed due to slow accrual (Pusztai 2006).

Baseline characteristics

Limited baseline data are available for many of these studies since they were only reported as abstracts. The median age of patients ranged from 46 to 57 years, which was comparable to the EGF100151 lapatinib trial (median age 52 years).

Table 5.32: Baseline characteristics for trastuzumab beyond progression prospective studies

Study	Characteristic	Population
H0659g (Tripathy 2004)‡#	Age (median, years) KPS ≥ 90 ER- / PR- Stage IV disease ≥ 3 metastatic sites	NR 50 (54%) NR NR 50 (54%)
Bangemann 2000 (Conference abstract)+	Age (median, years) KPS ≥ 90 ER- / PR- Stage IV disease ≥ 2 metastatic sites	NR NR NR NR 80%†
Suzuki 2003§	Age (median, years) KPS ≥ 90 ER- / PR- Stage IV disease ≥ 2 metastatic sites	52.5 NR 14 (58%) NR 10 (42%)
Miller 2005†	Age (median, years) KPS ≥ 90 ER- / PR- Stage IV disease ≥ 3 metastatic sites	52* NR NR NR 116 (50%)
Bartsch 2006§	Age (median, years) KPS ≥ 90 ER- / PR- Metastatic sites (median) ≥ 2 metastatic sites	46 NR NR 3 48 (89%)
HERMINE (Conference abstract, Extra 2006)‡	Age (median, years) KPS ≥ 90 ER- / PR- Stage IV disease ≥ 2 metastatic sites	52* NR NR NR NR

† All patients, including trastuzumab naïve patients
‡ Subgroup receiving more than one line of trastuzumab
§ All patients, all trastuzumab pretreated
+ Baseline of main trial (including trastuzumab naïve patients)
# Baseline of extension study
* Age is mean

Table 5.33: Baseline characteristics for trastuzumab beyond progression retrospective studies

Study	Characteristic	Population
Fountzilas 2003§ ++	Age (median, years) ECOG PS ≤ 1 ER- / PR- Stage IV disease ≥ 2 metastatic sites	54 78 (98%) 19 (24%) 1 (1%) 51 (64%)
García-Sáenz 2005† ++	Age (median, years) KPS ≥ 90 ER- / PR- Stage IV disease ≥ 2 metastatic sites	50.5 NR 20 (34%) NR 26.9%

Study	Characteristic	Population
Gelmon 2004† ++	Age (median, years) KPS ≥ 90 ER- Stage IV disease ≥ 2 metastatic sites	47 NR 45 (43%) NR NR
Montemurro 2006† ##	Age (median, years) KPS ≥ 90 ER-and/or PR- Stage IV disease ≥ 2 metastatic sites	53 NR 93 (50%) NR 118 (64%)
Stemmler 2005‡ ++	Age (median, years) KPS ≥ 90 ER- / PR- Stage IV disease ≥ 2 metastatic sites	57 NR 6 (26%) NR 21 (91%)
Tokajuk 2006† ##	Age (median, years) KPS ≥ 90 ER- / PR- Metastatic sites (median) < 2 metastatic sites	52 NR NR 2 9 (33%)

† All patients, including trastuzumab naïve patients
‡ Subgroup receiving more than one line of trastuzumab
§ All patients, all receiving more than one line of trastuzumab
++ At time of diagnosis/initiation of first trastuzumab therapy
Not clear when measured, may have been prior to first trastuzumab therapy

5.8.1.3. Capecitabine monotherapy

An RCT reported by Miller et al compared capecitabine alone with capecitabine in combination with bevacizumab, although only data from the capecitabine arm is presented in this submission (Miller 2005). The study included patients with metastatic breast cancer of whom only approximately 20% were HER2+. Those women who were HER2+ had, as part of the inclusion criteria, to have progressed on trastuzumab.

Baseline characteristics

The baseline characteristics of the capecitabine arm of the study were comparable to the lapatinib trial EGF100151.

Table 5.34: Baseline characteristics for capecitabine monotherapy arm (Miller 2005)

Study	Characteristic	Population
Miller 2005†	Age (median, years) ECOG PS ≤ 1 ER-positive PR-positive HER2-positive Stage IV disease ≥ 3 metastatic sites	52* 100% 51.7% 41.7% 20.4% NR 116 (50%)

* Age is mean; † All patients, including trastuzumab naïve patients

5.8.1.4. Vinorelbine monotherapy

No non-randomised studies investigating vinorelbine monotherapy in HER2+ patients previously treated with trastuzumab were identified.

Two protocols for randomised studies involving vinorelbine monotherapy were found ((i) Piccart-Gebhart 2004 [http://www.cancer.gov/clinicaltrials/EORTC-10001]; (ii) Pusztai 2005 [SWOG S0347, NCT00103233]). Both studies have now closed.

5.8.2. Critical appraisal of relevant non-RCTs

The critical appraisal for the lapatinib non-RCTs and the non-lapatinib non-RCTs are presented in Appendix 9.6.

Lapatinib
The lapatinib non-RCTs used lapatinib monotherapy rather than lapatinib plus capecitabine, the intervention being appraised. Two of the studies were conducted solely in the US. The CTEP study included patients with progressive brain metastases, whereas patients in the registration EGF100151 study had stable brain metastases.

Trastuzumab-containing therapy
The non-RCTs involving trastuzumab-based regimens were mostly either open trial extensions, observational studies or retrospective studies. Several of the studies involved small patient numbers or were conducted at single centres.

Capecitabine monotherapy
Miller et al was a well-conducted RCT comparing capecitabine monotherapy versus bevacizumab plus capecitabine in a mixed HER2+ and HER2- population; the combination arm is not relevant to this decision problem and therefore not included in the economic analyses.

5.8.3. Results of the relevant non-RCTs

5.8.3.1. Lapatinib therapy

Summarised efficacy results for the three lapatinib non-RCTs are presented in table 5.35. Safety data from these studies is discussed in section 5.7.2.

Studies EGF20002 and EGF20008 demonstrate modest activity of lapatinib monotherapy in patients with HER2+ advanced or metastatic breast cancer after treatment with multiple cytotoxic chemotherapies and trastuzumab (Blackwell 2005). Responses rates were lower than those observed in the EGF100151 study but it should be noted that the intervention was lapatinib monotherapy rather than lapatinib plus capecitabine (and hence these data have not been used in the economic analysis).

NCI CTEP6969 examined the efficacy of lapatinib in treating patients with progressive brain metastases following trastuzumab and radiation therapy. With only two partial responses in 39 patients, the study did not achieve the hypothesized level of activity. Nevertheless, evidence of clinical activity was observed (Table 5.35) and the investigators concluded that further exploration of lapatinib in HER2+ CNS disease was warranted (Lin 2006).

Table 5.35: Efficacy summary for lapatinib non-RCTs

Study	N	Tumour Response		Time to Progression (weeks) (95% CI)		Progression-free survival (weeks)	Median Overall Survival (weeks) (95% CI)
		Independent-evaluated n (%) (95% CI)	Investigator-evaluated n (%) (95% CI)	Independent-evaluated	Investigator-evaluated		
EGF20002 Data from CSR (Abstracts: Kaplan 2003; Blackwell 2004a; Blackwell 2004b; Blackwell 2005)	78	CR = 0 PR = 4 (5%) SD = 31 (40%) Response rate (CR or PR) = 5.1% (1.4%, 12.6%) CBR (CR or PR or SD $\geq$ 6 mo) = 9.0% (3.7%, 17.6%)	CR = 1 (1%) PR = 5 (6%) SD = 29 (37%) Response rate (CR or PR) = 7.7% (2.9%, 16.0%) CBR (CR or PR or SD $\geq$ 6 mo) = 14.1% (7.3%, 23.8%)	15.3	9.0	15.3	78.6 (56.9, 102.9)

Study	N	Tumour Response		Time to Progression (weeks) (95% CI)		Progression-free survival (weeks)	Median Overall Survival (weeks) (95% CI)
		Independent-evaluated n (%) (95% CI)	Investigator-evaluated n (%) (95% CI)	Independent-evaluated	Investigator-evaluated		
EGF20008 [Cohort A] Data from CSR (Abstracts: Burstein 2004; Blackwell 2005)	Coh-ort A: 140	CR = 0 PR = 2 (1%) SD = 46 (33%) Response rate (CR or PR) = 1.4% (0.2%, 5.1%) CBR (CR or PR or SD ≥ 6 mo) = 5.7% (2.5%, 10.9%)	CR = 3 (2%) PR = 3 (2%) SD = 38 (27%) Response rate (CR or PR) = 4.3% (1.6%, 9.1%) CBR (CR or PR or SD ≥ 6 mo) = 5.7% (2.5%, 10.9%)	9.1	NR	9.1	29.4 (22.9, 37.7)
NCI CTEP6969 Data from abstracts (Abstracts: Lin 2006; Van den Abbeele 2006)	39	-	CR in CNS = 0 PR in CNS = 2 (5.1%) Response rate in CNS (CR or PR) = 5.1% CR at non-CNS sites = 0 PR at non-CNS sites = 4 (10.2%)	-	3.02 (2.04, 3.68)	Progression-free in CNS at 16 weeks = 8 Progression-free in CNS at 24 weeks = 4*	6.57 (4.60, Infinity)

* one patient had non-CNS progression

5.8.3.2. Trastuzumab-containing regimens

The efficacy data reported in Table 5.36 relate only to patients who received trastuzumab beyond progression (i.e. second line and beyond). Where data were available for separate lines, the tabulated data is for second-line therapy. The results for the Gelmon study (Gelmon 2004) are combined data for patients progressing on trastuzumab plus vinorelbine, trastuzumab plus paclitaxel, or for trastuzumab alone.

Although the absence of a control group limits the validity of findings from these studies, some of the studies appeared well conducted and make a contribution to the evidence base. Safety data from these studies are discussed in section 5.7.5.

Table 5.36: Summary of key findings from trastuzumab beyond progression studies

Study	Interventions	Median TTP	CR N (%)	PR N (%)	SD N (%)	Response Rate	Median OS (mths)	Median PFS (mths)
Prospective studies								
H0659g	trastuzumab ± chemotherapy (N = 93[$])	-	3 (3%)	7 (8%)	-	11%	-	-
Bangemann 2000	trastuzumab + vinorelbine (n=10) trastuzumab + capecitabine (n=17) trastuzumab + docetaxel (n=9)	3 mths 3 mths 3.5 mths	-	-	(30%) (24%) (22%)	40% 53% 33%	-	-
Suzuki 2003	vinorelbine + trastuzumab (N=24)	92+ days	2 (8%)	8 (33%)	3 (13%)	42%	-	-
Bartsch 2006	trastuzumab ± chemotherapy (N = 54)	6 mths	(3.7%)	(22.2 %)	(42.6%)	-	-	-
HERMINE (Extra 2006)	Trastuzumab ± chemotherapy (N=107[$])	-	-	-	-	-	21.3	-
Retrospective studies								
Fountzilas 2003	trastuzumab ± chemotherapy (N = 80)	5.2 mths	3 (4%)	16 (20%)	22 (28%)	19 (24%)*	-	-

Study	Interventions	Median TTP	CR N (%)	PR N (%)	SD N (%)	Response Rate	Median OS (mths)	Median PFS (mths)
García-Sáenz 2005	trastuzumab + chemotherapy (N = 31[$])	3 mths	-	-	(12.9%)	25.8%	-	-
	Subgroups: trastuzumab + taxanes (N = 14)	-	-	-	-	28.6%	-	-
	trastuzumab + vinorelbine (N = 10)	-	-	-	-	20%	-	-
	trastuzumab + other chemotherapy (N = 7)	-	-	-	-	28.6%	-	-
Gelmon 2004	trastuzumab monotherapy (N = 11)	30.5 wks (N=10)	-	-	3	36% (4)	-	-
	trastuzumab + paclitaxel (N = 21)	24 wks (N=21)			6	38% (8)		
	trastuzumab + vinorelbine (N = 33)	26 wks (N=33)			8	27% (9)		
Montemurro 2006	trastuzumab + chemotherapy (N = 40[$])	6.3 mths	-	-	-	17.9%	30.1	-
Stemmler 2005	trastuzumab + chemotherapy (N = 23[$])	-	-	-	-	39.1%	62.4	-
Tokajuk 2006	trastuzumab + chemotherapy (N = 14[$])	5.1 mths	2 (14.3 %)	5 (35.7 %)	-	-	-	-

* Patients on second-line trastuzumab therapy; $ Subgroup treated after progression on trastuzumab

Pooling of TTP data

TTP was the most commonly reported time-to-event endpoint. A pooled median TTP was therefore estimated, first converting months TTP to weeks TTP for each study using the relationship [weeks=months x (52/12)]. Owing to the absence of data on the variance of the median TTP estimates, each study (or arm within study) was weighted by the number of subjects within the pooling process. A weighted standard deviation of the pooled estimate was calculated by taking the weighted sum of the squared differences from the pooled estimates. Given the pooled estimate of the median TTP (21.8 wks) and its corresponding standard deviation (1.2), a 95% CI was calculated for this pooled estimate (19.5 to 24.3 wks) assuming that median TTP would follow a lognormal distribution (Table 5.37).

Given the inconsistent reporting of results for individual regimens it was not feasible to differentiate between the efficacy of trastuzumab when given alone, or when given in combination with chemotherapy.

Table 5.37: Pooling estimates of median TTP in studies of trastuzumab beyond progression

Author (year)	Treatment	N	Median TTP (wks)
Continued trastuzumab			
Tripathy (2004)	T+/-CT	93	NR
HERMINE / Extra (2006)	T+/-CT	107	NR
Stemmler (2005)	T+/-CT	23	NR
Bangemenn (2000)	T+V	10	13.0
Bangemenn (2000)	T+C	17	13.0
Bangemenn (2000)	T+D	9	15.0
Suzuki (2003)	T+V	24	13.0
Gelmon (2004)	T+V	33	26.0
Gelmon (2004)	T+P	20	24.0
Gelmon (2004)	T-only	10	30.5
Fountzilas (2005)	T+/-CT	80	22.5
Garcia-Saenz (2005)	T+CT	31	13.0
Bartsch (2006)	T+CT	54	26.0
Montemurro (2006)	T+/-CT	40	27.3
Tokajuk (2006)	T+/-CT	14	22.1
Minimum			13.0
Maximum			30.5
Weighted mean			
Mean			21.8
SD			4.2
SE			1.2

Weighted mean calculated with X_i weighted by N_i. Weighted SD calculated with $(X_i-\mu)^2$ weighted by N_i. Weighted SE=Weighed SD/sqrt(N studies) SD_i for median TTP_is not available.
T=Trastuzumab, CT=chemotherapy, V=vinorelbine, C=capecitabine, D=docetaxel, P=paclitaxel, NR=not reported

It has not been possible to make direct or even indirect/mixed comparisons of the efficacy for lapatinib plus capecitabine versus continuation of trastuzumab from the available trial data because none of the trastuzumab studies contain the specific relevant comparisons. There is also limited data available on characteristics of patients after their first progression on trastuzumab. Therefore, comparisons of the efficacy data for trastuzumab beyond progression with that obtained for the treatment arms in the EFG100151 study are not adjusted and consideration must be given to the nature of the evidence. For this reason, sensitivity analyses around trastuzumab efficacy will be presented in the economic section.

The studies by Stemmler et al (Stemmler 2005), Montemurro et al (Montemurro 2006), Extra et al (Extra 2006) compared continuation of trastuzumab beyond progression versus discontinuation of trastuzumab. In the retrospective study by Montemurro, clinical outcomes were similar irrespective of whether trastuzumab was continued or not. The other two studies showed a significant benefit of continuing trastuzumab. Stemmler found that patients who received a trastuzumab-based regimen beyond progression survived significantly longer than those who received only one trastuzumab-based regimen for metastatic disease (62.4 vs. 38.5 months; p=0.01). In the prospective study by Extra (Extra 2006), patients who received multiple lines of trastuzumab beyond progression had a significant OS benefit

compared with those who stopped (OS 21.3 months (95% CI 17.9, 29.4) vs. 4.6 months (95% CI 2.8, 10.5); p=0.0001).

5.8.3.3. Capecitabine monotherapy

Efficacy results for the capecitabine arm of the study by Miller et al are summarised below (Miller 2005). The median PFS of 4.17 months was similar to that seen in the capecitabine arm of the EGF100151 study (17.6 weeks); however, it should be noted that these results are for a population in which only approximately 20% of patients were HER2+. Results for the HER2+ subset were not available separately so the data do not contribute to the economic analysis. Safety data from this study is discussed in section 5.7.5.

Table 5.38: Summary of key findings from the capecitabine monotherapy arm (Miller 2005)

Study	Interventions	Median TTP (mths)	CR N (%)	PR N (%)	SD N (%)	Response Rate	Median OS (mths)	Median PFS (mths)
Prospective studies								
Miller 2005	Capecitabine (N = 230)	-	-	--	-	9.1%	14.5	4.17

5.8.3.4. Vinorelbine monotherapy

As no published studies involving vinorelbine monotherapy were retrieved by the systematic review, an attempt was made to obtain an efficacy estimate for vinorelbine monotherapy relative to capecitabine monotherapy that could be extrapolated to this setting. A non-systematic search of MEDLINE was therefore undertaken for RCTs comparing capecitabine monotherapy with vinorelbine monotherapy in metastatic breast cancer but no studies were found.

A randomised study of capecitabine versus vinorelbine has been undertaken but has not been published. This RCT enrolled women with metastatic breast cancer previously treated with taxanes with or without anthracyclines (Piccart-Gebhart 2004; http://www.cancer.gov/clinicaltrials/EORTC-10001). [redacted]

In the NICE appraisal of capecitabine in locally advanced or MBC, neither the assessment group nor the manufacturer found any relevant comparative studies of capecitabine versus vinorelbine (Jones 2002). The NICE Appraisal Committee concluded that it was unlikely that capecitabine was less effective than vinorelbine (NICE TA no. 62). A number of other sources suggest that the two drugs have broadly similar efficacy for women with locally advanced or metastatic breast cancer that is resistant to anthracyclines and/or taxanes (Anonymous 2003; Seidman 2003).

5.9. Interpretation of clinical evidence

5.9.1. Provide a statement of the relevance of the evidence base to the decision problem.

Include a discussion of the relevance of the outcomes assessed in clinical trials to the benefits experienced by patients in practice.

The ultimate goals of treatment for patients with metastatic breast cancer are to delay disease progression and extend survival time with a manageable safety profile and an acceptable quality of life for patients. The decision problem in this appraisal was to assess the clinical (and cost) effectiveness of lapatinib plus capecitabine compared with other agents used in patients with HER2+ advanced/metastatic breast cancer who had relapsed following treatment with an anthracycline, a taxane and trastuzumab.

The pivotal registration trial (EFG100151) found a highly statistically significant increase in the primary endpoint of independently-assessed time to progression (TTP), in patients receiving lapatinib plus capecitabine compared with those on capecitabine alone. TTP is deemed to be a sensitive, clinically meaningful and appropriate endpoint in the advanced/metastatic setting (Di Leo 2003; EMEA 2005). An increase of approximately 50% in median TTP (8.5 week improvement) is of significant clinical benefit in this population whose disease is often rapidly progressing. Results also showed statistical significance in favour of lapatinib plus capecitabine for tumour response rate and progression-free survival (PFS). Although the detection of a survival difference has been impacted by the early termination of the study and the cross-over allowed, a trend towards a survival advantage has been observed (Figure 5.4).

The toxicity profile observed in the lapatinib plus capecitabine arm was manageable and consistent with the use of each agent, with no new safety concerns observed. In the overall lapatinib safety database, changes in LVEF associated with lapatinib occurred at a very low incidence (Perez 2006), consistent with that reported in a general population of cancer patients. In addition, there was no detriment to quality of life for patients receiving lapatinib plus capecitabine.

Patients with HER2+ advanced/metastatic breast cancer who have relapsed following trastuzumab treatment currently have few therapeutic options available to them and no alternative HER2-targeted therapy. The EGF100151 trial is the first and only RCT to have examined the effectiveness of continued HER2-suppression following progression on trastuzumab. It is therefore highly relevant to clinical practice that lapatinib, when added to capecitabine, was clearly shown to provide an efficacy advantage and to maintain quality of life, with no increase in toxicity, (consistent with the goals of management in metastatic breast cancer) in this area of unmet medical need. This was borne out by the recommendation of the IDMC to stop study enrolment at the time of the interim analysis and allow subjects on capecitabine alone to cross-over to lapatinib plus capecitabine.

Patients with HER2+ breast cancer treated with trastuzumab are at higher risk of developing brain metastases (Altaha 2004; Gabos 2006; Lin 2007). Breast cancer with brain metastases is a clinically challenging disease with no standard of care and limited treatment options available. It is therefore relevant to clinical practice that lapatinib has shown preliminary evidence of activity against brain metastases. In the EGF100151 study, lapatinib plus capecitabine significantly reduced the incidence of first relapse within the CNS compared with single-agent capecitabine (p=0.0445), suggesting a level of preventative action regarding brain metastases. Additionally, in a phase II study some partial clinical responses or extended stable disease were

seen in patients receiving lapatinib monotherapy who had progressive brain metastases following trastuzumab therapy (Lin 2006).

As previously highlighted, the lapatinib EGF100151 study was the only relevant RCT identified and the evidence base for comparators in this setting is unsurprisingly very limited. The studies identified were all non-randomised, mostly single-arm observational studies, a number of which were conducted retrospectively. The difficulties in interpreting their relevance are the uncontrolled study design, the almost complete lack of statistical dispersion data around any outcomes, the variable levels of anthracycline and/or taxane pre-treatment, and incomplete reporting of participant characteristics. Perhaps the most significant conclusion that can be drawn when interpreting the evidence base is the demonstrable need for proven treatment options in these patients facing unfavourable outcomes following progression on trastuzumab.

Due to limitations in the evidence base supporting treatments in this setting, it has been necessary to perform indirect comparisons using the non-randomised, non-comparative data sources identified.

In the absence of directly comparative data, single-agent capecitabine has previously been assumed to have similar effectiveness to single-agent vinorelbine (NICE TA no. 62; Anonymous 2003; Seidman 2003). It is therefore reasonable to assume that the relative benefits of lapatinib plus capecitabine compared with capecitabine alone can be extended to single-agent vinorelbine in this setting.

To provide a comparison of the clinical effectiveness of lapatinib plus capecitabine versus trastuzumab continued beyond progression, the progression data from the latter studies were pooled. This yielded a median TTP estimate of 21.8 weeks (95% CI 19.5, 24.3) for trastuzumab beyond progression, which lies between the median TTPs for capecitabine and for lapatinib plus capecitabine.

As discussed earlier in this submission, patients who are most likely to receive continued trastuzumab are those in whom the drug still appears to be having some effect, despite progression (for example those patients with stable disease at most sites with progression at an isolated site, including those with brain metastases (Montemurro 2006, Dendrite data – Appendix 9.4, Kirsch 2005), those with few metastases in the soft tissues or bone (Garcia-Saenz 2005)) and those with a good response to an initial trastuzumab regimen (Montemurro 2006). These patients are likely to be included within the population recruited to EGF100151 (with the exception of those with progressive brain metastases who were excluded). This population is expected to form a greater proportion of the patients within the studies involving trastuzumab beyond progression. Limited data on patient characteristics have been reported in the latter studies but, where available, suggests that the EGF100151 and trastuzumab beyond progression populations are broadly similar (based on their age, performance status and number of metastatic sites).

Although patients with brain metastases are likely to have a worse prognosis than those without brain metastases, patients with a single site of progression may have a better prognosis than those with multiple lesions. Given these effects are in opposite directions, there is no obvious reason to believe that the effectiveness of lapatinib plus capecitabine in a population who may be likely to receive continued trastuzumab would be significantly different from that seen in the EGF100151 population. However, sensitivity analyses in the economics section will address varying assumptions around the relative effectiveness of trastuzumab beyond progression versus lapatinib plus capecitabine.

In summary, lapatinib plus capecitabine provides a rational and effective option as next line of treatment for patients whose disease has progressed on or following

trastuzumab. The efficacy advantages seen are real and relevant for these patients for whom there are currently no specifically proven therapeutic options.

5.9.2. Identify any factors that may influence the applicability of study results to patients in routine clinical practice;

For example, issues relating to conduct of the trial versus clinical practice or to the choice of eligible agents. What proportion of the evidence base is for the dose(s) given in the SPC?

The EGF100151 trial is the only RCT evaluating lapatinib plus capecitabine. The population included in the trial were required to have had an anthracycline and a taxane in either the adjuvant or metastatic settings, plus trastuzumab for advanced or metastatic disease. This is slightly more restrictive than the likely indication statement for lapatinib which does not stipulate the setting for prior trastuzumab usage.

The dosage used in the trial was lapatinib 1250mg once daily continuously *plus* capecitabine 2000mg/m^2/day, on days 1-14 of a 21-day cycle. This was established as the optimally tolerated regimen for the combination in a phase I study (De Bono 2003; Schwartz 2004) and is consistent with the lapatinib SmPC.

Single-agent capecitabine was an appropriate comparator for the study as it is widely used in this setting in UK clinical practice (Appendix 9.4). The capecitabine dosage in the monotherapy arm was based on that recommended on the capecitabine SmPC of 2500mg/m2/day (Xeloda SmPC).

Approximately 60% of patients in both arms of the study had received their last dose of trastuzumab within the previous 8 weeks. It has been suggested that the activity of lapatinib may have been enhanced by the persistence of trastuzumab in the body due to its long half-life (Sonpavde 2007). However, an analysis of efficacy split by the time interval from last dose of trastuzumab to randomisation (≤ 8 weeks vs. > 8 weeks) showed that the presence of any residual trastuzumab had minimal influence on the response to lapatinib (Geyer 2007).

The demographic characteristics of the patients in the EGF100151 RCT were representative of patients in this setting in the UK. Median age of the total study population was 52 years which is similar to that seen in patients who have progressed on trastuzumab after previous anthracycline- and taxane- based regimens in UK practice (median age within the range 56-60 years, Appendix 9.4). Patients in the study had an ECOG Performance Status of 0 (60%) or 1 (40%); again this is consistent with that seen in patients in this setting in clinical practice (Appendix 9.4).

The study was conducted at sites across North and South America, South Africa, Hong Kong, Australia and Europe, including 12 UK sites which drew approximately 10% of the study population. There are no obvious reasons why any unidentified geographical differences would make the results of the study inapplicable to England and Wales.

In the EGF100151 trial, patients were selected for good cardiac function (LVEF within institutional range of normal); this is consistent with the proposed SmPC which requires a baseline LVEF within the institution's normal limits. The SmPC also specifies that LVEF is evaluated prior to initiating lapatinib and during treatment consistent with the monitoring undertaken in the study. LVEF monitoring in metastatic breast cancer in UK clinical practice is variable depending on locality. The schedule of cardiac monitoring adopted by clinicians for lapatinib is likely to greater than that undertaken for single-agent capecitabine or vinorelbine, but is unlikely to be more than that routinely undertaken for trastuzumab in clinical practice.

Only a small number of patients with brain metastases were recruited in the EGF100151 study due to the requirement for stable brain metastases (asymptomatic and off medication for ≥ 3 months). Patient receiving lapatinib plus capecitabine in practice may be more likely to have progressive brain metastases, particularly given the requirement for progression on trastuzumab, and the fact that about 30% of patients treated with trastuzumab for metastatic disease have been reported to develop brain metastases (Bendell 2003; Lin 2004).

In relation to the comparator evidence, the majority of evidence for the continuation of trastuzumab beyond disease progression is from observational studies and is therefore likely to be representative of the use of trastuzumab beyond progression in clinical practice, although it must be acknowledged that these studies have mostly been conducted outside the UK. Additionally, in the trastuzumab beyond progression studies there were differing eligibility criteria (and/or patient characteristics) relating to prior therapy with anthracyclines and/or taxanes whereas the likely indication for lapatinib specifies prior treatment with both an anthracycline and a taxane in line with the EGF100151 study.

In summary, it is reasonable to assume that the results achieved with lapatinib plus capecitabine after introduction into routine clinical practice in England and Wales will not differ significantly from those observed in the EGF100151 trial.

5.9.3. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted.

Figure 2.2 provides a decision flow chart to assess patient eligibility for lapatinib plus capecitabine in the population discussed in this submission (see Section 2.2). Patients eligible for lapatinib must have received an anthracycline and a taxane in either the adjuvant or metastatic settings, and trastuzumab for metastatic disease. As discussed in sections 2 and 4 of this submission, the main regimens currently used in UK clinical practice in patients progressing on trastuzumab are single-agent chemotherapies (primarily capecitabine or vinorelbine) and trastuzumab continued alone or in combination with either of these agents.

As discussed previously, patients who may be more likely to receive continued trastuzumab are those in whom the drug still appears to be having some effect, despite progression, e.g. those patients with stable disease at most sites with progression at an isolated site, including those with brain metastases (Montemurro 2006, Dendrite data – Appendix 9.4, Kirsch 2005), those with few metastases in the soft tissues or bone (Garcia-Saenz 2005) and those with a good response to an initial trastuzumab regimen (Montemurro 2006). Such patients would be suitable for lapatinib plus capecitabine.

6. Cost effectiveness

6.1. Published cost-effectiveness evaluations

6.1.1. Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

A systematic literature review was conducted with the aim of identifying all published economic evaluations of lapatinib for the treatment of advanced breast cancer.

Identification of appropriate databases

Searches were conducted on the following clinical and health economics databases: Medline and Medline (R) In-Process, Embase, Health Economic Evaluation Database (HEED), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database and Cumulative Index to Nursing & Allied Health Literature (CINAHL). No restrictions were applied to the publication date within the searches. All the databases were accessed and searched on March 4th, 2007.

Search strategy

The systematic search strategy was designed to recover only those publications that refer to economic evaluations of lapatinib. All relevant commercial and industrial names of the drug were identified and incorporated into the search syntax. An appropriate filter for identifying economic evaluation studies was used for the majority of searches. However, for some of the databases this filter was not used as only a few records were expected to be retrieved by searching on the drug name only, thus manual filtering was feasible. The search syntax, including terms and combinations of them, are presented in Appendix 9.3 of this submission.

Inclusion criteria

The identified publications would be considered relevant to the decision problem addressed within this report only if:

- the study refers to lapatinib AND
- economic evaluations AND
- the study population related to women with advanced or metastatic or recurrent breast cancer, who have undergone previous treatment.

6.1.2. Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

The search resulted in 82 records. The results were imported in reference management software. All abstracts were assessed according to the pre-specified inclusion criteria described in Section 6.1.1. None of the abstracts met the inclusion

criteria, as none of the abstracts referred to economic evaluations. Consequently, no published cost-effectiveness studies were considered relevant to this review.

6.2. De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained.

6.2.1. Technology

How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

The likely indication for the technology under consideration is: lapatinib, in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2) and who have received prior therapy including trastuzumab, an anthracycline and a taxane. The proposed dosage is lapatinib 1250mg once daily on a continuous basis plus capecitabine 2000mg/m^2/ day, taken in two doses 12 hours apart, on days 1–14 of a 21-day cycle. Both treatments are orally administered.

Within the economic evaluation, lapatinib plus capecitabine is assumed to continue until either documented disease progression or death. This continuation assumption is also applied to all other treatment strategies considered within the base case of the economic evaluation.

6.2.2. Patients

6.2.2.1. What group(s) of patients is/are included in the economic evaluation?

Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The relevant population for the economic evaluation is women with advanced or metastatic breast cancer whose tumours overexpress HER2 and who have received prior therapy including trastuzumab in the metastatic setting. This population reflects the population of the EGF100151 study and is anticipated to form the basis of the licensed indication for lapatinib in combination with capecitabine. The populations included in the economic evaluation are believed to relate directly to the specified decision problem.

6.2.2.2. Was the analysis carried out for any subgroups of patients?

If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?

Within the EGF100151 trial formal prospective subgroup analysis was undertaken according to two baseline prognostic factors: age and race. Meaningful conclusions could not be drawn for these specific patient subgroups (see Section 5.4.6). In addition, response rates were examined according to stratification factor and a number of covariates were examined in a proportional hazards model with TTP. Neither of these approaches identified subgroups of patients (See Section 5.4.4. and 5.4.5). Consequently, subgroup analyses were not undertaken within this economic evaluation.

The subpopulation that is most likely to receive continued trastuzumab beyond progression was not modelled separately but is assumed to be contained within the evidence base for lapatinib plus capecitabine, and for trastuzumab beyond progression, and will be further discussed in Section 6.3.4.2.

6.2.2.3. Were any obvious subgroups not considered?

If so, which ones, and why were they not considered?

Patients with brain metastases are an obvious sub-group but the economic evaluation does not consider them specifically as study EGF100151 included only a small number of patients with brain metastases at baseline (see Section 5.4.3), so there is no efficacy data in this group on which to base an analysis.

6.2.2.4. At what points do patients 'enter' and 'exit' the evaluation?

Do these points differ between treatment regimens? If so, how and why?

The health economic model uses a survival modelling methodology to estimate the expected time to disease progression and death. All outcomes and costs are evaluated over a lifetime horizon beginning with the start of treatment (or initial progression on trastuzumab for the continued trastuzumab monotherapy strategy). Costs and health outcomes are evaluated over a period of 1,825 days (5-years); at the end of this period, less than 1% of patients remain alive (see Section 6.2.6, Figures 6.4 and 6.6). Therefore this time horizon approximates a lifetime projection. The time to progression and death differs according to treatment strategy, and is dependent on time-to-event data sourced from the EGF100151 trial and from non-randomised studies (see Section 5.8.3).

6.2.3. Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

Five relevant options for the treatment of women following progression on trastuzumab for HER2+ metastatic breast cancer were considered and are summarised in Table 6.1:

1. Capecitabine monotherapy. Capecitabine is assumed to be given at the standard recommended dose (Xeloda SmPC) of 2500mg/m^2 daily on days 1-14 of a 21 day cycle.
2. Vinorelbine monotherapy. The recommended dosage of vinorelbine is 25-30mg/m^2 weekly (Navelbine SmPC). Within this economic analysis, vinorelbine is assumed to be administered at the lower end of the dose range, at 25mg/m^2 once weekly. This represents a conservative assumption.
3. Continued trastuzumab given alongside vinorelbine. The recommended dosage for trastuzumab administered as monotherapy is a weekly infusion at a dose of 2mg/kg (Herceptin SmPC); this is assumed within the health economic model. The base case model assumes that patients do not receive an initial loading dose (4mg/kg), however, this is explored within the sensitivity analysis (see Section 6.3.3). As with treatment strategy 2, the model assumes that vinorelbine is administered at the lower end of the dose range, at 25mg/m^2 once weekly.
4. Continued trastuzumab given alongside capecitabine. The model assumes that trastuzumab is given as in option 3. When used in combination with trastuzumab, capecitabine is assumed to be given at a dose of 2500mg/m^2 daily for 14 days within a 21 day cycle (NCT00148876, German Breast Group study 26).

5. Continued trastuzumab given as monotherapy as delivered in the combination therapies in options 3 and 4.

Table 6.1 Treatment regimens included in the cost-effectiveness model

Treatment regimen	Regimen component	Dose and schedule	Administration	Unit price
(1) Lapatinib plus capecitabine	Lapatinib	1250mg lapatinib daily on a continuous basis	oral tablet	£11.00 per tablet
	Capecitabine	2000 mg/m^2 capecitabine daily for days 1-14 of a 3-week cycle	oral tablet	£295.06 (500 mg, 120-tab pack) (BNF)
(2) Capecitabine monotherapy	Capecitabine	2500 mg/m^2 capecitabine daily for days 1-14 of a 3-week cycle	oral tablet	£295.06 (500 mg, 120-tab pack) (BNF)
(3) Vinorelbine monotherapy	Vinorelbine	25mg/m^2 vinorelbine weekly	intravenous bolus	£139.70 (5mL vial, 10 mg/mL) (Personal communication: Wockhardt)
(4) Trastuzumab plus vinorelbine	Trastuzumab	*Maintenance dose* 2mg/kg trastuzumab weekly	intravenous infusion	£407.40 (150mg vial) (BNF)
	Vinorelbine	25mg/m^2 vinorelbine weekly	intravenous bolus	£139.70 (5mL vial, 10 mg/mL) (Personal communication: Wockhardt)
(5) Trastuzumab plus capecitabine	Trastuzumab	*Maintenance dose* 2mg/kg trastuzumab weekly	intravenous infusion	£407.40 (150mg vial) (BNF)
	Capecitabine	2500 mg/m^2 capecitabine daily for days 1-14 of a 3-week cycle	oral tablet	£295.06 (500 mg, 120-tab pack) (BNF)
(6) Trastuzumab monotherapy	Trastuzumab	*Maintenance dose* 2mg/kg trastuzumab weekly	intravenous infusion	£407.40 (150mg vial) (BNF)

The first comparison (versus capecitabine monotherapy) is consistent with the two treatment strategies compared in study EGF100151. However, in routine clinical practice in the UK, many HER2+ patients who progress while receiving treatment with trastuzumab for metastatic disease continue to receive trastuzumab beyond disease progression either alone or in combination with chemotherapy agents. In addition, single-agent vinorelbine is also considered as a relevant treatment option in such patients (see Section 4.1 and Appendix 9.4).

There is some uncertainty about the most commonly used dosing regimens for vinorelbine and trastuzumab. Some patients are prescribed vinorelbine only on days 1 and 8 of a 21 day cycle, despite being recommended once-weekly in the SmPC (Navelbine SmPC). Also, the number of cycles may be limited, for example to 6. Trastuzumab is also given at 6mg/kg every 3 weeks in the UK, although this is not in line with the SmPC for metastatic breast cancer (Herceptin SmPC). These different dosing options are explored in the sensitivity analyses in Section 6.3.3.

Empirical justification for the inclusion of these comparator regimens is provided in Appendix 9.4.

6.2.4. Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The economic analysis has been undertaken from the perspective of the NHS and Personal Social Services (PSS). However, PSS costs have not been identified as key drivers of differences between treatments in the cost of caring for this population. Therefore no PSS costs are included in the modelling.

6.2.5. Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

All relevant costs and health outcomes are evaluated over a lifetime horizon. The model time horizon therefore relates to the point at which a patient becomes eligible for treatment with lapatinib (following disease progression on prior therapy including trastuzumab, an anthracycline and a taxane) until death. The health economic model uses a 5-year time frame as patients are not expected to survive beyond this point; the median overall survival duration within study EGF100151 was less than 68 weeks for the two treatment groups (03 April 2006 cut-off, ITT analysis). Within the health economic model the probability of remaining alive beyond this time frame is negligible, irrespective of treatment group.

6.2.6. Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

6.2.6.1. Please provide the following:

A description of the model type.
A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.
A list of all variables that includes their value, range (distribution) and source.
A separate list of all assumptions and a justification for each assumption.

(For a list of all variables please see Appendix 9.8)

Modelling the cost-effectiveness of lapatinib plus capecitabine in the treatment of HER2+ metastatic breast cancer following progression on trastuzumab

Overview of model

The health economic model presented within this submission estimates the incremental cost-effectiveness of lapatinib plus capecitabine as compared against other standard treatments used in the treatment of women with HER2+ advanced or metastatic breast cancer who have received prior treatment with trastuzumab. The development of the cost-effectiveness model has been based closely upon the methodology adopted with the recent assessment of the cost-effectiveness of bevacizumab in the treatment of metastatic colorectal cancer (Tappenden 2006a) and explicitly addresses key methodological problems associated with modelling cancer interventions (Tappenden 2006b). The health economic model includes six

treatment regimens. Details of these regimens and their respective dose and administration schedules are presented in Table 6.1.

Modelling methodology

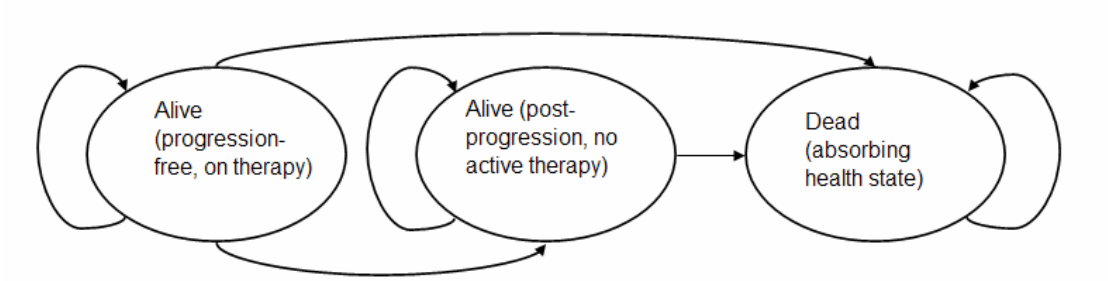
The model uses a survival modelling approach within a decision-analytic framework to estimate the costs and health outcomes associated with each of the six included treatment regimens. Costs and health outcomes for each of the regimens are then compared incrementally. The modelling methodology employed within the cost-effectiveness model presented here is essentially analogous to the state transition (Markov) approach, as the model estimates costs and health outcomes based upon time spent in discrete states of health. A simplified schematic of the cost-effectiveness model is presented in Figure 6.1. The model includes three conceptual health states:

(1) Alive prior to disease progression

(2) Alive following disease progression

(3) Dead

Figure 6.1 Simple schematic of the cost-effectiveness model



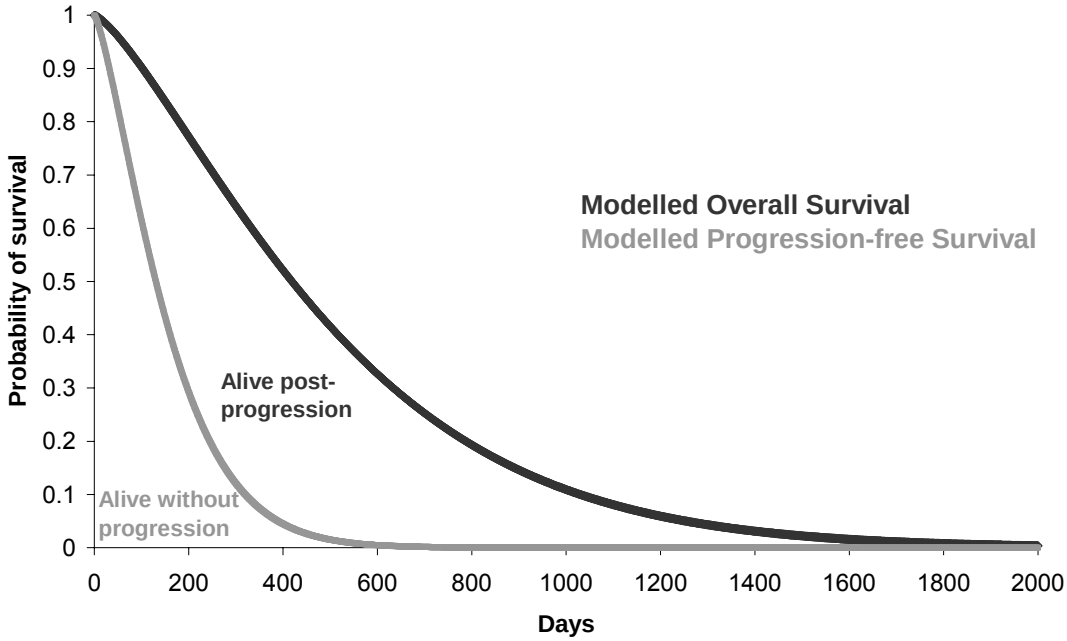
Patients enter the model in the Alive progression-free health state and receive one of the active therapy regimens until they subsequently experience disease progression and/or death. In reality, patients have already experienced disease progression on prior therapy at the point of inception into the model, but on initiating further treatment as they enter the model they are considered to be progression free for this line of treatment. Patients are assumed to continue receiving one of the six included treatment regimens for the duration of time spent without subsequent disease progression. Per-diem values for health utilities and costs were calculated and applied to the time (days) that patients were free of progression and post progression (i.e. no variation in daily cost by time previously spent in state).

The cost-effectiveness model is very similar to a state transition (Markov) model with states defined based on vital status and, for those remaining alive, disease progression. However, unlike a Markov model, in which transitions between states are modelled explicitly based on transition probabilities, the cost-effectiveness model calculates the proportion of patients in each treatment group that is expected to reside in each of the states based on the estimated survival functions for progression-free survival and overall survival. Rather than estimating transition probabilities (i.e. from alive-no progression to post-progression or death, and from post-progression to death) for use within the model, area under the curve analysis is used to estimate the mean duration of time spent without disease progression and the mean duration of time spent alive. The difference between these two curves provides a direct estimate of the mean survival duration following disease

progression. This approach allows for the direct modelling of progression-free and overall survival data from study EGF100151 (see Figures 6.2 to 6.6) without the assumptions that would be required to obtain such consistency within the Markov model framework (for example, the model does not need to assume that all patients must progress prior to death).

Information concerning subsequent-line or salvage chemotherapy usage following disease progression on the study interventions was not collected within study EGF100151. Whilst patients may receive subsequent-line or salvage chemotherapies following disease progression, there is no evidence to suggest that resource use would be different between the treatment groups included in the model. Therefore, the costs associated with any subsequent-line or salvage chemotherapies are not explicitly included in the cost-effectiveness model.

Figure 6.2 Schematic of approach for estimating time in model health states



In order to estimate measures of effectiveness, the proportion of patients receiving each treatment strategy, j, who are expected to be alive at each time, t (i.e., overall survival, [OS(j,t)]), and alive and progression free at each time, t (progression-free survival, [PFS(j,t)]), are estimated for each treatment strategy. In the model, time *t* represents days since initiation of therapy (or days from first progression for patients receiving continued trastuzumab therapy). For each treatment option, the proportion of patients alive and post-progression at each time, *t* (post-progression survival, [PPS(j,t)]), is calculated by subtracting PFS(j,t) from OS(j,t)t. Expected (i.e., mean) progression-free life years (PFLYs), post-progression life years (PPLYs), and overall life years (LYs) for each strategy, j (E[PFS(j)], E[PPS(j)], and E[OS(j)], respectively) are calculated as the sum of PFS(j,t), PPS(j,t), and OS(j,t) over the model time horizon, T, as follows:

$$E[PFS(j)] = \sum_{t=1}^{T} PFS(j,t)$$

$$E[PPS(j)] = \sum_{t=1}^{T} PPS(j,t)$$

$$E[OS(j)] = \sum_{t=1}^{T} OS(j,t)$$

It should be noted that progression-free survival is used within the model instead of time to progression, as the former describes the probability of being alive without disease progression over time (i.e. death is treated as an event). This is not the case for time to progression, where death events are censored.

Model parameters

Modelling health outcomes for capecitabine monotherapy

Effectiveness outcomes for patients receiving capecitabine monotherapy were based on empirical time-to-event data (progression-free survival and overall survival) collected within study EGF100151. Statistical analyses were undertaken using SAS statistical software Version 9.1 (SAS Institute Inc., North Carolina). As the empirical Kaplan Meier curves for progression-free survival and overall survival outcomes within study EGF100151 were subject to a degree of censoring, regression analysis was used to fit Weibull curves to the empirical patient-level time-to-event outcomes. The Weibull survivor functions, S(t), used within the cost-effectiveness model are based upon the formulation put forward by Collett (Collett 2003) as shown below.

$$S(t) = \exp\{\lambda t^{\gamma}\}$$

where λ describes the Weibull scale parameter, γ describes the Weibull shape parameter, and t is time.

Table 6.2 shows the resulting parameters for the capecitabine monotherapy Weibull models of overall survival and progression-free survival. The data used in the health economic analysis relate to the 03 April 2006 cut-off for study EGF100151, using independently assessed time-to-event outcomes.

Table 6.2 Weibull curve parameters for capecitabine monotherapy group based on statistical analysis of study EGF100151

Parameter	Mean	Standard deviation	Distribution
Overall survival model			
Weibull scale parameter, lambda (λ)	0.0019	0.00017	Bootstrap estimates
Weibull shape parameter, gamma (γ)	1.4846	0.10722	Bootstrap estimates
Progression-free survival model			
Weibull scale parameter, lambda (λ)	0.0058	0.00044	Bootstrap estimates
Weibull shape parameter, gamma (γ)	1.3920	0.06319	Bootstrap estimates

Figures 6.3 and 6.4 show a comparison of the observed Kaplan-Meier estimates of progression-free survival and overall survival for the capecitabine monotherapy group. The figures suggest that the Weibull regression models provide a good fit against the empirical data.

Figure 6.3 Observed and fitted Weibull model of progression-free survival for capecitabine monotherapy

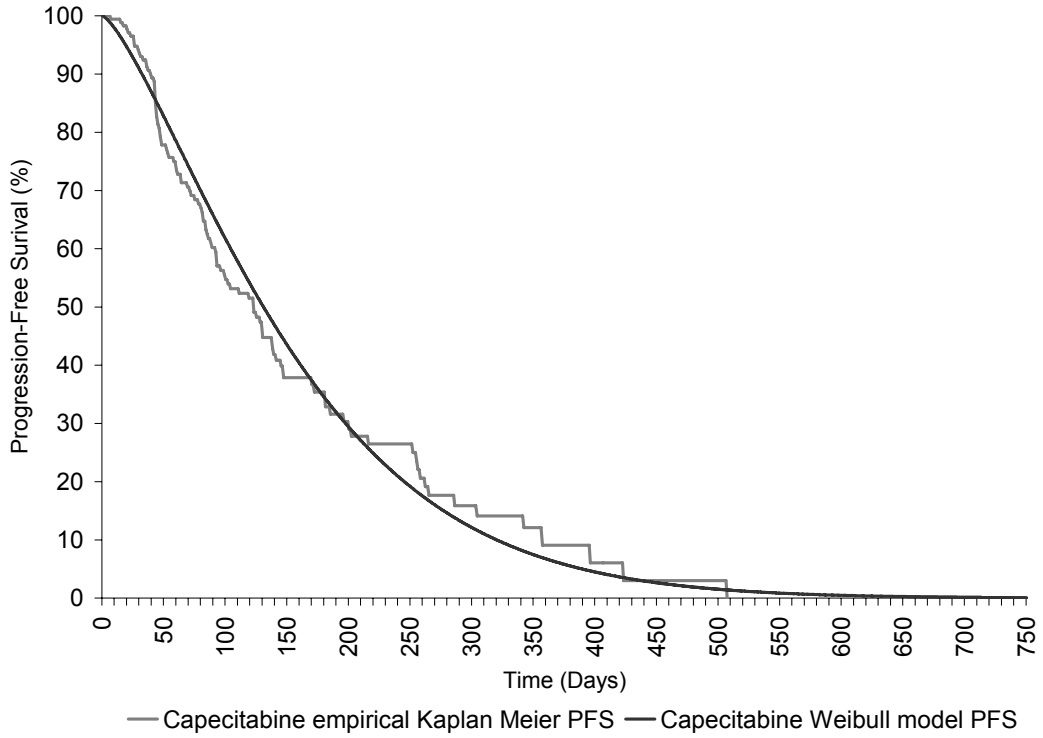
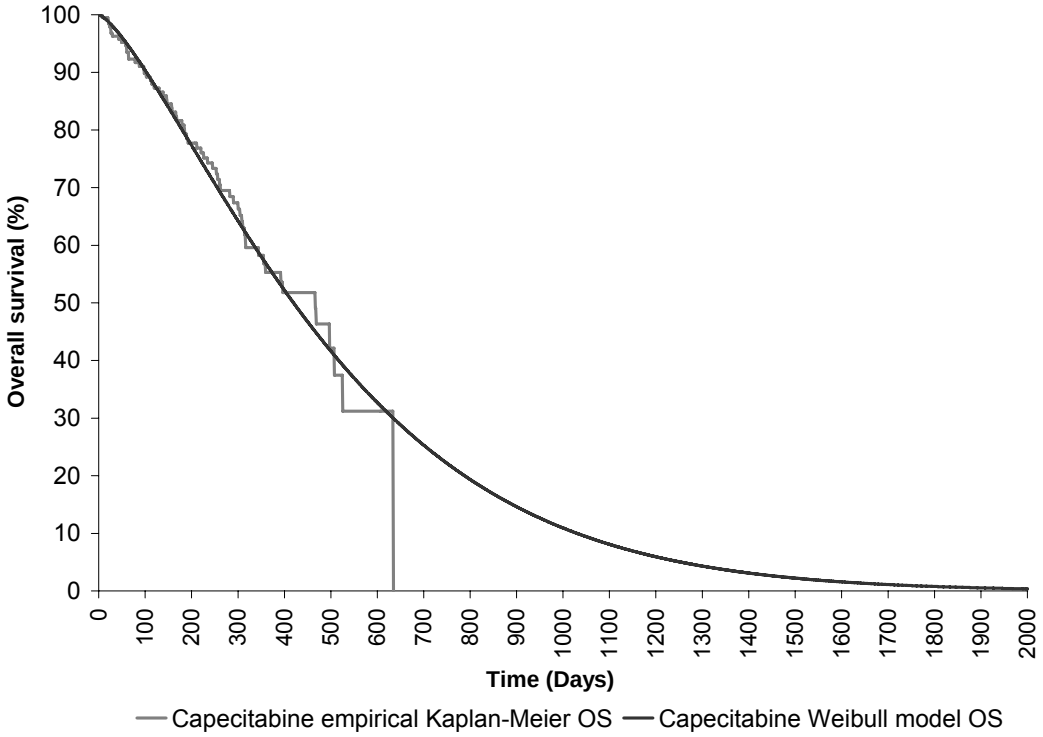


Figure 6.4 Observed and fitted Weibull model of overall survival for capecitabine monotherapy



As mean progression-free survival, post-progression survival and overall survival are correlated, parameters of the survival curves for progression-free survival and overall survival were sampled from the empirical joint bootstrap distribution of these

parameters within the EGF100151 study for use in the probabilistic sensitivity analysis.

Other parametric forms are available to model time-to-event data, for example, exponential or gamma distributions. The goodness of fit of these distributions was explored during the model development process. Firstly, the application of an exponential distribution was considered. Within this model, the gamma parameter is held constant at 1. As the more general Weibull regression shows that gamma is greater than 1 (see Table 6.2), the exponential model did not provide an adequate fit to the empirical data. Subsequently, the use of a gamma distribution was also considered. The gamma distribution did provide a good fit to the empirical data, however improvements over the Weibull models were not readily discernable. Consequently these two alternative parametric forms were rejected. In addition, the Holander and Proschan C* test for goodness of fit of specific distributions with known parameters was undertaken for each of the Weibull models used in the economic analysis. The null hypothesis is that the data follow Weibull distributions with base-case estimates of lambda, gamma, and HR (as appropriate). The results of this analysis suggested that in no instance is $p<0.05$, which in turn suggested that in no instance was there insufficient evidence to conclude that the time-to-event data are not drawn from Weibull distributions with base-case estimates of lambda, gamma, and a hazard ratio.

Modelling the relative effectiveness of lapatinib plus capecitabine

Expected progression-free survival and overall survival outcomes for patients receiving lapatinib plus capecitabine were also sourced from the EGF100151 trial. The relative hazard of experiencing an event (either disease progression or mortality) within the lapatinib plus capecitabine group was assumed to be proportional to the event hazard rates within the capecitabine monotherapy group. Overall survival and progression-free survival outcomes for patients receiving lapatinib plus capecitabine were therefore modelled by applying a relative hazard ratio to the baseline hazard for the capecitabine monotherapy treatment group. As such, the hazard rates for the lapatinib plus capecitabine group, HPFS[1,t] and HOS[1,t], are constrained to be constant multiples of the hazard rates for capecitabine only, HPFS[2,t] and HOS[2,t] respectively, i.e.

$$H^{PFS}[1,t] = H^{PFS}[2,t] \times HR^{PFS}_{1vs2}$$

$$H^{OS}[1,t] = H^{OS}[2,t] \times HR^{OS}_{1vs2}$$

where HR^{PFS}_{1vs2} and HR^{OS}_{1vs2} are the hazard ratios for lapatinib plus capecitabine (j=1) versus capecitabine only (j=2) for PFS and OS respectively. Survival functions for lapatinib plus capecitabine and capecitabine only are calculated as follows:

$$PFS[1,t] = e^{-(\lambda^{PFS} HR^{PFS}_{1vs2})t^{\gamma^{PFS}}} \qquad PFS[2,t] = e^{-(\lambda^{PFS}t)^{\gamma^{PFS}}}$$

$$OS[1,t] = e^{-(\lambda^{OS} HR^{OS}_{1vs2})t^{\gamma^{OS}}} \qquad OS[2,t] = e^{-(\lambda^{OS}t)^{\gamma^{OS}}}$$

The three parameters of each model (i.e., λPFS, γPFS, and HR^{PFS}_{1vs2} and λOS ,γOS, and HR^{OS}_{1vs2}) were estimated using an accelerated failure time (AFT) regression model whereby treatment group was entered as a covariate in the regression model. The resulting hazard ratios describing the relative benefit of lapatinib plus capecitabine versus capecitabine monotherapy are shown in Table 6.3. These are

similar to the hazard ratios calculated from the 03 April 2006 cut-off data from the study (see Section 5.4.2) which were 0.55 for PFS (95% CI, 0.41-0.74) and 0.78 for OS (95% CI, 0.55-1.12).

Table 6.3 Relative hazard ratios for lapatinib plus capecitabine versus capecitabine monotherapy

Parameter	*Value*	*Standard deviation*	*Distribution*
Progression-free survival hazard ratio	0.6085	0.06885	Bootstrap estimates
Overall survival hazard ratio	0.8344	0.10455	Bootstrap estimates

Table 6.4 compares the PFS and OS data derived from the Kaplan-Meier curves of EGF100151 against the modelled data. Medians were reported in Section 5.4 but cost-effectiveness is calculated based on the expected (i.e. mean) values. Although the median PFS and OS estimates obtained by the models are somewhat different from the Kaplan-Meier estimates, especially for OS, the means at the last failure time (obtained by summing the area under the curves up to that point) are more similar, suggesting that although the models may differ slightly at the medians, on balance, they fit the curves well.

Table 6.4 PFS and OS data derived from the Kaplan-Meier curves of EGF100151

Outcome measure	Data type	Lapatinib plus capecitabine	Capecitabine-only	Difference
Median PFS (days)	EGF100151 data (Kaplan-Meier)	189	122	67
	Modelled data (Proportional hazards regression)	217	132	85
Mean PFS (days)	EGF100151 data (Kaplan-Meier)	259	160	99
	Modelled data (Proportional hazards regression)	258	157	101
Median OS (days)	EGF100151 data (Kaplan-Meier)	473	465	8
	Modelled data To end of FU (last failure time) (Proportional hazards regression)	488	407	81
Mean OS (days	EGF100151 data (Kaplan-Meier)	459	404	55
	Modelled data To end of FU (last failure time) (Proportional hazards regression)	440	400	40

Diagrammatic representations of the modelled curves shown in Figures 6.5 and 6.6 suggest that the assumption of proportional hazards provides a good fit to the empirical progression-free and overall survival curves. The validity of the proportional hazards assumption was explored by performing i) correlation tests between the ranked failure times and the Schoenfeld residuals (p=.5101 and p=.1342 for PFS and OS respectively); ii) the supremum test for the proportional hazards assumption (p=.6590 and p=.7578) (PROC PHREG ASSESS) (Lin 1993) iii) comparisons of hazard ratios for L+C vs C-only by quarter post-randomization. These tests provided no strong evidence of non-proportionality.

Figure 6.5 Observed and fitted Weibull model of progression-free survival for lapatinib plus capecitabine

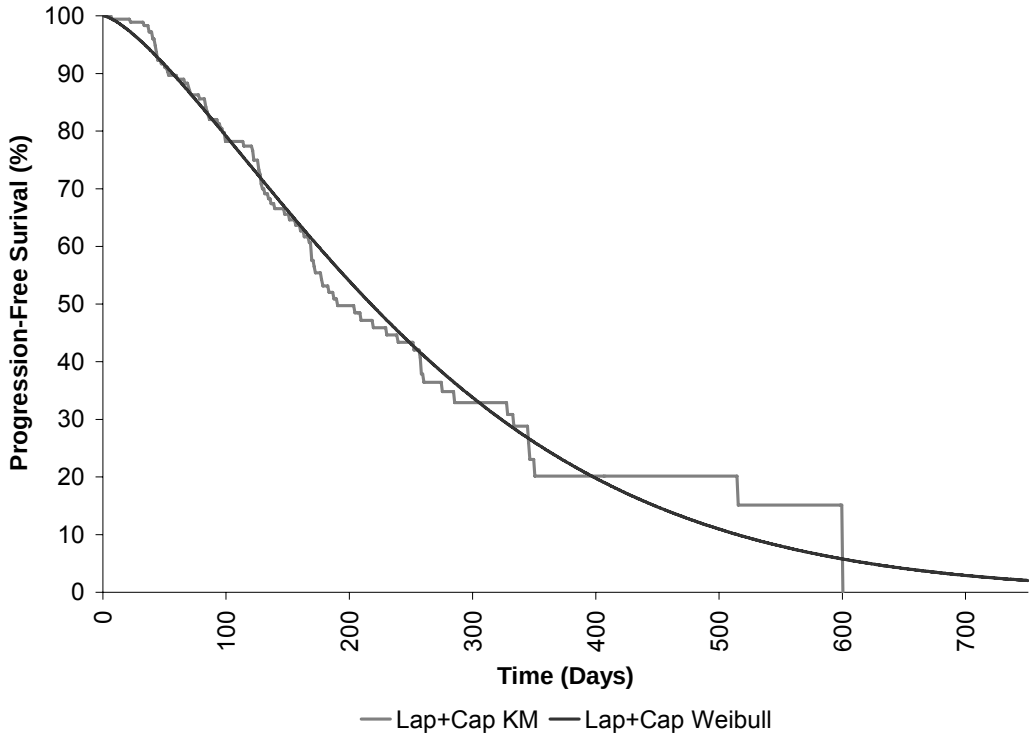
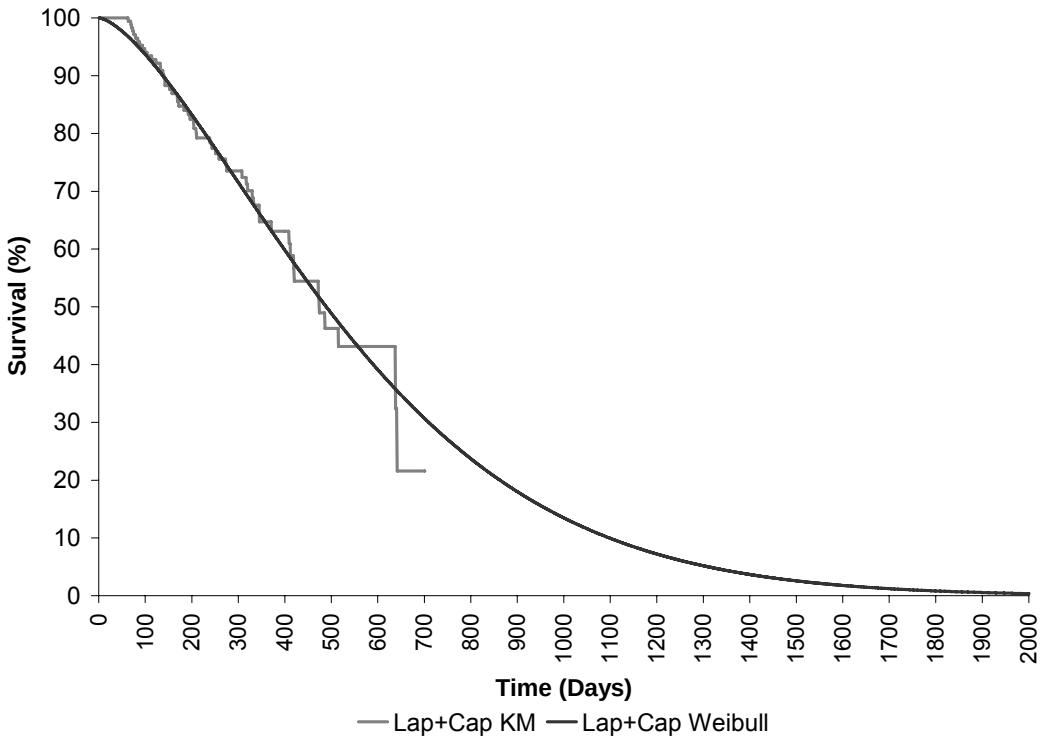


Figure 6.6 Observed and fitted Weibull model of overall survival for lapatinib plus capecitabine



The impact of using independent, rather than proportional hazards upon the incremental cost-effectiveness of lapatinib plus capecitabine is presented in the sensitivity analysis (see Section 6.3.3).

Modelling the relative effectiveness of trastuzumab with or without chemotherapy

There is no direct evidence for lapatinib plus capecitabine against trastuzumab-containing therapy in the treatment of women with HER2+ metastatic breast cancer following progression on trastuzumab regimens. Expected progression-free survival durations for women receiving trastuzumab-based therapies were estimated using data from published studies of the efficacy and safety of trastuzumab in patients with HER2+ metastatic breast cancer who had received one or more prior courses of trastuzumab therapy. All studies from a systematic review (described in Section 5.1 and 5.2) that reported data on time to progression or progression-free survival among women who received further trastuzumab treatment after one or more prior courses of trastuzumab were identified.

Eight studies met these inclusion criteria, representing a total of 342 patients (Bartsch 2006; Montemurro 2006; Tokajuk 2006; Garcia-Saenz 2005; Gelmon 2004; Fountzilas 2003; Bangemann 2000). All 8 studies reported median TTP with ranges and/or 95% confidence intervals commonly reported, but none reported measures of variance. Only two studies reported results by adjunctive chemotherapy received (Gelmon 2004; Bangemann 2000) whilst the remaining studies reported results for trastuzumab as monotherapy or in combination with various chemotherapies.

Given the limited data through which to estimate progression-free survival durations for the trastuzumab-containing regimens of interest, some simplifying assumptions were made:

1. All trastuzumab based regimens are equally effective within the model patient population at this line of treatment;
2. Median time to progression is approximately equal to median progression-free survival in patients with HER2+ metastatic breast cancer.
3. PFS for trastuzumab-containing therapies follows the same functional form (Weibull) as for capecitabine monotherapy.

Assumption 2 is supported by the work of Sherill et al (Sherill 2007; RTI Health Solutions report for GSK, data on file) who found that distinctions between definitions for TTP or PFS were not made consistently and regression results (by treatment groups) describing the relationship between TTP/PFS and OS were comparable regardless of which endpoint was reported.

A pooled median TTP estimate of 21.8 weeks was produced (see Section 5.8.3.2). We then solved for the hazard ratio versus capecitabine monotherapy in the proportional hazards Weibull model for progression-free survival (estimated from the EGF100151 study) that would yield the pooled estimate of median time to progression. The same procedure was repeated for the upper and lower bounds of the 95%CI of median time to progression values. This yielded an implied hazard ratio for continued trastuzumab therapy versus capecitabine monotherapy of 0.87 (95%CI 0.78-0.97). The standard deviation of the estimated hazard ratio was calculated to be 0.05 assuming that the HR would follow a lognormal distribution (i.e., SD(HR)=[ln(HR)–ln(HR95%CI-lower)]/norminv(0.975)). The expected post-progression survival duration for trastuzumab-containing regimens is assumed to be the same as for lapatinib plus capecitabine. The effectiveness of trastuzumab-containing therapies is explored in the sensitivity analyses reported in Section 6.3.3.

Modelling the relative effectiveness of vinorelbine monotherapy

In the absence of clinical evidence for vinorelbine in this indication, the model assumes that progression-free survival and overall survival outcomes for patients receiving vinorelbine monotherapy are equivalent to those observed within the capecitabine monotherapy arm of study EGF100151 (see Section 5.8.3.4. This assumption is in line with assertions stated concerning the relative effectiveness of capecitabine and vinorelbine within existing NICE guidance (NICE TA no. 62).

To summarise, median time to progression for lapatinib plus capecitabine was 27.1 weeks (from EGF1000151), for capecitabine or vinorelbine was 18.6 weeks (from EGF100151), and for trastuzumab regimens was estimated at 21.8 weeks (from pooled analysis above).

Modelling health-related utility values

The cost-effectiveness model assumes that a patient's level of health-related quality of life is dependent on whether they have experienced disease progression, or whether they are progression-free. Within the base case analysis, the model assumes that a patient has a higher level of health-related quality of life (HRQoL) prior to disease progression (Lloyd 2006; Earle 2000) and that health utilities do not differ according to treatments received. For the pre-progression health state, a health utility score was derived directly from the EGF100151 trial.

Health utilities were assessed within study EGF100151 using both the EQ-5D health classification questionnaire and the visual analogue thermometer. The health economic analysis presented within this submission is based upon the former, as this is a well validated preference-based instrument, and as such is in keeping with NICE's Reference Case. EQ-5D utility scores were valued using the UK tariff reported by Dolan (Dolan 1997). Within the EGF100151 trial, assessments using the EQ-5D were required by the protocol only until withdrawal of study medication, i.e. until disease progression. Analyses of utility values obtained during the study (i.e. in the pre-progression health state) using the last-observation carried forward (LOCF) imputation rule suggested that EQ-5D utility scores were similar in the two trial groups and remained relatively stable over the duration of follow-up (excluding the concluding visit at which utility values declined in both groups presumably reflecting the onset of underlying disease progression). This is in line with analyses presented in Section 5.4.7 and pre-progression utility values were therefore assumed be independent of treatment strategy and time since initiation of therapy.

A utility for the pre-progression state was estimated by calculating the mean utility score for each patient across all assessments prior to the concluding visit and then calculating the mean (SE) across patients, irrespective of treatment group, weighting each patient by the number of assessments. This methodology differs from that described in Section 5.4.7 as it does not employ imputation and data from patients who were withdrawn from treatment at a scheduled visit is excluded. The pre-progression utility estimate estimated by this methodology and applied within the model was 0.69.

Utility values relating to the post-progression disease state were largely unavailable from the trial, and the generaliseability of those values that are available are subject to a considerable degree of uncertainty and potential bias. Relevant utility estimates were therefore obtained from a study reported by Lloyd et al (Lloyd 2006). Within this study, UK societal preferences were elicited for various metastatic breast cancer states including stable disease, treatment response, progression and adverse events using the standard gamble (SG) technique. Lloyd et al reported the use of logit model describing the coefficients according to tumour status, age and the presence of

adverse events. This model was reproduced probabilistically using the mean population age from EGF100151 to generate an estimate of the relative difference between the mean utility for the disease progression state and the stable disease state together with an estimate of the standard error of the mean. Over 1,000 random iterations, this analysis suggested a mean relative ratio for post- versus pre-progression of 0.68 and a standard error of 0.08. This relative ratio was then applied to the EGF100151 pre-progression utility score. Hence, the model assumes that the mean post-progression utility score is 0.69*0.68=0.47.

Each treatment regimen included in the model is associated with adverse events which may negatively impact upon a patient's health-related quality of life (although analyses presented in Section 5.4.7 show that any differences between capecitabine and lapatinb plus capecitabine regimens are not significant enough to be reflected in differences in the mean quality of life scores). Regimen-specific data relating to adverse event disutilities are not available from the EGF100151 trial, and are only partially available from the literature (for example, Lloyd 2006; Earle 2000). Including such disutilities in the model would require a number of assumptions about durations of adverse events and the independent or co-dependent impact of such events on disutility. Further, such events are already captured for the capecitabine plus lapatinib and capecitabine monotherapy treatment groups in the EGF100151 pre-progression utility estimate; further inclusion would therefore lead to a downward biasing of resulting utility estimates due to double counting. For these reasons, further disutilities associated with adverse events are not included in the model.

It is also noteworthy that there may be a benefit in health-related quality of life for patients receiving oral as opposed to infusional regimens, relating specifically to greater patient freedom, lesser burden of treatment, and reduced hospital attendances. The impact of such differences in health-related quality of life between oral and infusional treatment regimens is excluded from the base case analysis, but is explored within the sensitivity analysis (see Section 6.3.3). Health utility values assumed within the model are summarised in Table 6.5.

Table 6.5 Health utility scores used within the cost-effectiveness model

Health state	Mean utility	Standard error	Distribution	Source
Pre-progression	0.694	0.01	Beta	EGF100151
Post-progression	0.47 (relative % decrement = 0.32)	0.08 (applied to relative reduction)	Beta	Lloyd et al, 2006 estimate applied to pre-progression utility from study EGF100151

Modelling costs and resource use

The cost-effectiveness model distinguishes between the costs of care incurred whilst patients are free from disease progression (and are receiving active treatment), and the costs associated with those resources consumed following disease progression. Where available, chemotherapy resource use estimates were sourced from study EGF100151; these have been supplemented by unit cost estimates available from the British National Formulary (BNF No. 52), NICE Technology Assessment Reports, (Tappenden 2006a; Hind 2005; Ward 2006) and current literature (Remak 2004). The study by Remak et al estimated lifetime cost of treatment for patients in the UK presenting with stage IV breast cancer (Remak 2004). To determine patterns of treatment and resource use in the absence of direct observational data, a cancer physician panel was surveyed.

As study EGF100151 did not evaluate the efficacy of trastuzumab-containing regimens or vinorelbine monotherapy, the model assumes that that these regimens

are given according to the dosing schedules described by Burstein et al (Burstein 2001), and the ongoing NCT00148876 trial.

The model includes only direct costs to the NHS. All costs are valued at 2006 prices. Where 2006 prices were not available, these have been uplifted using the Hospital and Community Services Prices Index (Curtis 2006). Where costs have been uplifted to 2006 prices, these are shown in parentheses [ ].

Nine groups of resource and cost components are included in the health economic model:

1. Drug acquisition;
2. Hospital resources for chemotherapy administration;
3. Pharmacy costs;
4. Management of adverse events;
5. Diagnostic and laboratory tests;
6. Clinical consultation;
7. Radiotherapy;
8. Other special interventions e.g. blood transfusions;
9. Monitoring of patients receiving trastuzumab and lapatinib.

1. Drug acquisition costs

Unit costs per mg for capecitabine, vinorelbine and trastuzumab were taken from the BNF No. 52. The unit cost for lapatinib was sourced directly from GSK. In keeping with recent guidance issued by NICE, Value Added Tax (VAT) was not included in acquisition cost estimates within the health economic model. For oral regimens (lapatinib and capecitabine), the model estimates drug acquisition costs based upon a mean cost per tablet, whilst for infusional regimens (trastuzumab and vinorelbine) drug acquisition costs are estimated according to the mean cost per mg. Acquisition costs used within the model are shown in Table 6.6.

Table 6.6 Drug acquisition costs for the treatment regimens included in the health economic model

Drug component	Cost per pack/vial	Mgs per pack/vial	Relevant unit	Cost per unit
Lapatinib	£770.00	17,500	per tablet	£11.00
Capecitabine	£295.06	60,000	per tablet	£2.46
Trastuzumab	£407.40	150	per mg	£2.72
Vinorelbine	£139.70	50	per mg	£2.80

Relative dose intensity adjustments

The model generates estimates of the costs of active treatment, including drug acquisition and administration, based on the planned daily dosage, the planned days of treatment per day without disease progression, and the mean progression-free days projected using survival analysis. However, patients may not receive the planned daily dosage due to dosage adjustment, and actual days of treatment may not equal planned days of treatment due to drug holidays (skipped doses) or early discontinuation (i.e. prior to disease progression). Furthermore, the cost-effectiveness model uses data on IRC-assessed progression-free survival from study EGF100151 to estimate survival functions, whereas study medication was terminated in the trial at the investigators' discretion based on investigator-assessed progression-free survival. As the Kaplan-Meier estimated independently-assessed progression-free survival duration was greater than that derived from investigator assessment, it is necessary to include in the model some adjustments for this difference to ensure that costs of active treatment are representative.

The model therefore includes two dose adjustment factors:

RDI for daily dosage - adjusts for the difference in actual dose prescribed versus the planned daily dosage, and affects only the costs of study medications (the cost of administration is assumed to be independent of daily dosage).

RDI for progression-free days treated - adjusts for the difference between actual days of therapy received and Independent Review Committee (IRC)-assessed progression-free survival, including (i) the difference due to skipped doses/early discontinuation i.e. missed days of therapy and (ii) the difference between investigator- and IRC-assessed progression-free survival i.e. days difference between a patient stopping therapy based on investigator-assessed progression and when they would have stopped therapy if awaiting notification of IRC-assessed progression. RDI for progression-free days treated affects both the cost of study medications and the cost of drug administration.

For the lapatinib plus capecitabine versus capecitabine monotherapy comparison, the RDI for daily dosage for each treatment group and study therapy was calculated based on the ratio of the mean daily dose received to the planned daily dose. The planned daily dose for each treatment group and study therapy was obtained from the EGF100151 Clinical Study Report (CSR). The mean daily dose received for each treatment group and study therapy was calculated as the sum of the product of actual/received daily dose times days of therapy received for each study drug administration divided by the sum of days of therapy received over all study drug administrations.

RDI data were not available for the indirect comparisons. However, in the interests of ensuring that the economic comparisons remain fair, it was necessary to adjust RDI parameters for these treatment regimens. For the indirect comparisons with trastuzumab-containing therapy, the model assumes the RDIs for trastuzumab would be the same as that for lapatinib in the lapatinib plus capecitabine comparison, while that for adjunctive chemotherapy would be the same as that for capecitabine in the lapatinib plus capecitabine comparison. For the trastuzumab monotherapy and vinorelbine monotherapy indirect comparisons, the model assumes that the RDI parameters would be the same as that for capecitabine monotherapy in study EGF100151. These are conservative assumptions for the IV therapies (and against the lapatinib plus capecitabine intervention) as one might expect concordance with an IV regimen to be higher than with a self-administered oral regimen.

Table 6.7 shows the estimated mean RDI parameters for the six treatment regimens included in the model (bootstrap standard errors are shown in brackets). Normal distributions were used to describe the uncertainty surrounding these parameters within the probabilistic sensitivity analysis. The impact of assuming 100% RDI for all treatments is explored in deterministic sensitivity analyses (see Section 6.3.3).

Table 6.7 Relative dose intensity estimates used within the cost-effectiveness model

Treatment regimen	Regimen component	RDI for daily dosage	RDI for days treated without disease progression	Source
Lapatinib plus capecitabine	Lapatinib	0.99 (0.004)	0.80 (0.077)	Study EGF100151
	Capecitabine	0.89 (0.017)	0.77 (0.075)	
Capecitabine monotherapy	Capecitabine	0.87 (0.014)	0.94 (0.072)	
Vinorelbine	Vinorelbine	0.87 (0.014)	0.94 (0.072)	Assumption based on

Treatment regimen	Regimen component	RDI for daily dosage	RDI for days treated without disease progression	Source
monotherapy				study EGF100151
Trastuzumab plus vinorelbine	Trastuzumab	0.99 (0.004)	0.80 (0.077)	
	Vinorelbine	0.89 (0.017)	0.77 (0.075)	
Trastuzumab plus capecitabine	Trastuzumab	0.99 (0.004)	0.80 (0.077)	
	Capecitabine	0.89 (0.017)	0.77 (0.075)	
Trastuzumab monotherapy	Trastuzumab (monotherapy)	0.87 (0.014)	0.94 (0.072)	

Treatment wastage

Treatment wastage is an important consideration for patients receiving infusional trastuzumab-containing therapy. Maintenance doses of trastuzumab are administered at a dose of 2mg/kg. As trastuzumab is packaged in 150mg vials, two vials are required for patients with a body mass greater than 75kg. In such instances, the remainder of the vial left unused would be discarded (or in a small number of cases the dose would be capped at the nearest full vial although this is not often possible). The model assumes a mean body mass of 68.9kg and a mean body surface area of 1.77m^2 based on the characteristics of the study population included in trial EGF100151. Based on the distribution of patients' body mass within trial EGF100151, the model estimates the weighted mean number of vials required for each maintenance dose of trastuzumab. This process was repeated for vinorelbine.

The costs of oral therapies include wastage for those patients who discontinue therapy before completing their last prescription for such therapy. To calculate wastage for oral therapy, the model calculates the number of units (tablets) in each prescription (planned dosage) based on the estimated number of days of therapy per prescription, the mg per tablet, the daily dose, and the assumed proportion of days of therapy remaining for the last prescription. The cost of wasted medication is added to the total cost of medication. The discounted cost of wasted medication is calculated by multiplying the undiscounted cost by the ratio of the discounted progression-free survival duration to the undiscounted progression-free survival duration.

The impact of excluding drug wastage on the incremental cost-effectiveness of lapatinib plus capecitabine is explored in the sensitivity analysis (see Section 6.3.3).

Subsequent-line/salvage chemotherapy

The costs associated with any subsequent-line or salvage chemotherapies following disease progression are not included in the cost-effectiveness analysis. This was discussed earlier in section 6.2.1.1 'Modelling methodology'.

2. Administration costs

Oral chemotherapies (lapatinib and capecitabine) are not associated with a cost of hospital administration. Instead the model assumes that these costs are included in the pharmacy preparation and dispensing costs and clinical consultation costs. Administration costs which require hospital attendance and clinician's time are assumed to be relevant only to the trastuzumab- or vinorelbine-containing treatment strategies; these hospital attendances are assumed to take place in an outpatient setting. The cost of an outpatient appointment for patients receiving chemotherapy was taken from the NHS Reference Costs 2006; the cost of a chemotherapy attendance excluding treatment costs was estimated to be £207.22 (Inter-Quartile Range = £171 to £277) (NHS Reference Costs 2006). This chemotherapy administration cost is assumed to be applied equally to all trastuzumab-containing

regimens. As vinorelbine requires less administration time than trastuzumab, the hospital attendance cost for vinorelbine administration is assumed to be 25% of the NHS Reference Cost value (cost=£51.81).

This chemotherapy administration cost was sampled using a lognormal distribution within the probabilistic sensitivity analysis.

3. Pharmacy costs

Estimated pharmacy costs per cycle of treatment are presented in Table 6.8. These estimates are based on pharmacy cost estimates sourced from the Christie Hospital NHS Trust, as detailed in two recent NICE Technology Assessment Reports (Tappenden 2006a; Hind 2005). The model assumes that the handling cost is £23.00 for a simple i.v. infusion, £38.00 for a complex i.v. infusion, and £12.00 for oral therapies. These pharmacy costs are assumed to include preparation time and dispensing. These costs are assumed to relate to 2006 values and therefore have not been inflated. The table also shows the estimated mean cost per day of treatment for each regimen component. These costs are direct inputs into the model and describe the pharmacy cost each day the patient receives treatment. For example, capecitabine is given daily for 14-days within a 21-day cycle, hence the pharmacy cost per day of use is calculated as £12.00/14 = 0.86.

Table 6.8 Pharmacy costs used within the health economic model

Treatment regimen	Oral components per cycle	Simple i.v. components per cycle	Complex i.v. components per cycle	Pharmacy cost per cycle	Cost per day of use
Lapatinib plus capecitabine	2	0	0	£24.00	Lapatinib=£0.57 Capecitabine=£0.86
Capecitabine monotherapy	1	0	0	£12.00	Capecitabine=£0.86
Trastuzumab plus vinorelbine	0	1	1	£61.00	Trastuzumab=£38.00 Vinorelbine=£23.00
Trastuzumab plus capecitabine	1	0	1	£50.00	Trastuzumab=£38.00 Capecitabine=£0.86
Trastuzumab monotherapy	0	0	1	£38.00	Trastuzumab=£38.00
Vinorelbine monotherapy	0	1	0	£23.00	Vinorelbine=£23.00

4. Management of adverse events and other hospitalisations

Within the base case analysis, the model assumes that the monthly costs associated with the management of adverse events are the same for each of the six treatment regimens. The impact of differential costs for the management of adverse events associated with each of the six included treatment regimens is considered in the deterministic sensitivity analysis (see Section 6.3.3).

The cost of managing adverse events includes the cost of hospital admissions and the costs of other non-cytotoxic medications used to resolve these events. Estimates for both cost components were taken from a costing study reported by Remak (Remak 2004). Within the model, the costs of adverse events and hospital admissions are assumed to be relevant to both the active treatment phase, as well as the remaining duration of life following disease progression. The cost of medications for managing adverse events is assumed to be £54.09 [£56.95] per month whilst patients are receiving active treatment, and £62.90 [£66.23] per month following

disease progression. The cost of other hospital admissions besides those associated with therapy administration is assumed to be £56.25 [£59.23] per month during the active phase of treatment, and £157.40 [£165.74] following disease progression.

Lognormal distributions were used to describe the uncertainty surrounding the costs of adverse events and hospitalisation within the probabilistic sensitivity analysis. As Remak et al (Remak 2004) only mean estimates for these costs, the probabilistic sensitivity analysis uses standard errors based on the assumption that the upper and lower confidence bounds are equal to 1.25/0.75 x mean cost estimates.

5. Diagnostic and laboratory tests

The cost of scans and laboratory tests were also taken from Remak et al (Remak 2004). Resource use and costs per month associated with scans and diagnostic tests are assumed to be the same for each treatment regimen. Prior to progression, an estimate of £227.63 [£239.69] per month is assumed; following disease progression, a cost of £77.77 [£81.89] per month is assumed.

Lognormal distributions were used to describe the uncertainty surrounding the costs of scans and laboratory tests within the probabilistic sensitivity analysis. As Remak et al only give mean estimates for these costs (Remak 2004), the probabilistic sensitivity analysis uses a standard error based on the assumption that the upper and lower confidence bounds are equal to 1.25/0.75 x mean cost estimate.

6. Clinical consultation

The costs of clinical consultation over and above those included in the chemotherapy administration costs were taken from Remak et al (Remak 2004). The authors report a cost of £82.90 [£87.29] per month during the pre-progression follow-up phase, which includes day case attendances, GP, specialist and nurse visits. This is likely to be a slight overestimate for infusional regimens, as hospital attendances for therapy administration have been already been accounted for in the model. Following disease progression, the model assumes a cost of £255.20 [£268.72] per month; this cost includes district nurse visits, MacMillan nurse visits and specialist visits.

Lognormal distributions were used to describe the uncertainty surrounding the costs of consultations within the probabilistic sensitivity analysis. Again, the probabilistic sensitivity analysis uses a standard error based on the assumption that the upper and lower confidence bounds are equal to 1.25/0.75 x mean cost.

7. Radiotherapy

Prior to disease progression this is assumed to cost £19.78 [£20.83] per month; following disease progression, this is assumed to cost £17.80 [£18.74] per month. Radiotherapy resource use and costs per month are assumed to be the same for each treatment regimen.

Lognormal distributions were used to describe the uncertainty surrounding the costs of radiotherapy within the probabilistic sensitivity analysis. The probabilistic sensitivity analysis uses a standard error based on the assumption that the upper and lower confidence bounds are equal to 1.25/0.75 x mean cost.

8. Special interventions

Patients may also receive various other interventions not included above, for example, blood transfusions. Again, owing to a lack of evidence to the contrary, these costs are assumed to be the same for the lapatinib, capecitabine, trastuzumab and vinorelbine regimens. Prior to disease progression, special interventions are

assumed to cost £29.25 [£30.80] per month; following disease progression, other special interventions are assumed to cost £101.66 [£107.04] (Remak 2004).

Lognormal distributions were used to describe the uncertainty surrounding the costs of these additional interventions within the probabilistic sensitivity analysis. The probabilistic sensitivity analysis uses a standard error based on the assumption that the upper and lower confidence bounds are equal to 1.25/0.75 x mean cost.

9. Monitoring of patients receiving trastuzumab and lapatinib

The use of trastuzumab is associated with an increase in risk of cardiotoxicity. It has been recommended that patients undergo regular monitoring whilst receiving treatment with trastuzumab. This is usually done using either Echocardiogram (ECHO) tests or MUltiple Gated Acquisition scan (MUGA) tests once every three months. Two thirds of the scans are assumed to be done using ECHO at a cost of £120 per test, with the remaining third being done using MUGA at a cost of £258. The corresponding monthly estimate is therefore £55.33 (calculated as [0.67*£120 + 0.33*£258]/3) (Ward 2006). Since the administration of lapatinib is likely to require cardiac monitoring the costs for monitoring are assumed to be the same for lapatinib plus capecitabine and trastuzumab.

A lognormal distribution was used to describe the uncertainty surrounding monitoring costs within the probabilistic sensitivity analysis. The probabilistic sensitivity analysis uses a standard error based on the assumption that the upper and lower confidence bounds are equal to 1.25/0.75 x mean cost.

Summary of model cost inputs

Table 6.9 presents a summary of cost parameters and distributions used in the health economic model updated to 2006 prices. Standard errors surrounding mean cost parameter values are shown in parentheses.

Table 6.9 Summary of model cost parameters

Cost/resource parameter	Phase of treatment		Distribution assumed	Source (year)
	Progression-free – mean cost (standard error)	Post-progression – mean cost (standard error)		
Unit cost lapatinib (per tablet)	£11.00	n/a	n/a	GSK
Unit cost of capecitabine (per tablet)	£2.46	n/a	n/a	BNF 52 (2006)
Unit cost trastuzumab (per mg)	£2.72	n/a	n/a	BNF 52 (2006)
Unit cost vinorelbine (per mg)	£2.79	n/a	n/a	Personal communication (Wockhardt UK)
Pharmacy costs lapatinib (per day of use)	£0.571 (n/a)	n/a	n/a	Derived from Tappenden (2006a)
Pharmacy costs capecitabine (per day of use)	£0.857 (n/a)	n/a	n/a	Derived from Tappenden (2006a)
Pharmacy costs trastuzumab (per day of use)	£38.00 (n/a)	n/a	n/a	Derived from Tappenden (2006a)
Pharmacy costs vinorelbine (per day of use)	£23.00 (n/a)	n/a	n/a	Derived from Tappenden (2006a)
Hospital administration costs for trastuzumab (per day of use)	£207.22 (£26.92)	n/a	Lognormal	Ward (2006)
Hospital administration costs for vinorelbine (per day of use)	£51.81 (£6.73)	n/a	Lognormal	Assumption
Monitoring costs for lapatinib and	£55.33 (£7.06)	n/a	Lognormal	Ward (2006)

Cost/resource parameter	Phase of treatment		Distribution assumed	Source (year)
	Progression-free – mean cost (standard error)	Post-progression – mean cost (standard error)		
trastuzumab (per month)				
Other medications to manage adverse events (per month)	£56.95 (£7.26)	£66.23 (£8.45)	Lognormal	Remak (2004)
Clinical consultation/Visits (per month)	£87.29 (£11.13)	£268.72 (£34.28)	Lognormal	Remak (2004)
Hospitalisation (per month)	£59.23 (£7.55)	£165.74 (£21.14)	Lognormal	Remak (2004)
Diagnostics (per month)	£239.69 (£30.57)	£81.89 (£10.45)	Lognormal	Remak (2004)
Radiotherapy (per month)	£20.83 (£2.66)	£18.74 (£2.39)	Lognormal	Remak (2004)
Other special interventions (per month)	£30.80 (£3.93)	£107.04 (£13.65)	Lognormal	Remak (2004)

List of model assumptions

Assumptions surrounding the modelling of health outcomes

- The model assumes that the hazard of experiencing an event (disease progression or death) for patients receiving lapatinib plus capecitabine is proportional to the event hazard rate for patients receiving capecitabine monotherapy.
- The progression-free survival benefit associated with trastuzumab-containing regimens is assumed to be proportional to the progression-free survival benefit of lapatinib plus capecitabine. Following disease progression, the duration of post-progression survival is assumed to be equivalent between trastuzumab-containing regimens and lapatinib plus capecitabine.
- The hazard ratio for progression-free survival for patients receiving trastuzumab-containing regimens is assumed to be independent of adjunctive chemotherapies given alongside trastuzumab.
- Progression-free survival and overall survival durations for patients receiving vinorelbine monotherapy are assumed to be equivalent to those for patients receiving capecitabine monotherapy.
- Health-related quality of life is assumed to be influenced primarily by the presence or absence of disease progression.
- Owing to a lack of evidence, the impact of adverse events on a patient's level of health-related quality of life is assumed to be independent of the treatment regimen received. It is assumed that the impact of adverse events related to lapatinib and capecitabine on utility is contained within the reported values.

Assumptions surrounding resource use and costs

- The model assumes that the average patient has a mean body mass of 68.9kg and a mean body surface area of 1.77m^2.
- Patients undergo the same diagnostic and laboratory tests, at the same frequency, irrespective of treatment regimen.
- The cost of scans and laboratory tests per month is the same irrespective of previous active treatments.
- Trastuzumab is assumed to be given as an IV infusion, whilst vinorelbine is given as a bolus IV push.
- Orally administered therapies, i.e. capecitabine and lapatinib, are not associated with an administration cost; administration costs for these therapies are included within pharmacy preparation and dispensing time. Infusional therapies are associated with an additional hospital administration cost.

- Relative dose intensity, which is used to calculate acquisition costs, is assumed to be lower than 100% for all drugs based on RDI estimates for combination therapy and monotherapy within study EGF100151.
- The dosage of capecitabine when used in combination with trastuzumab is assumed to be 2500mg/m^2 daily for 14 days within a 21 day cycle (NCT00148876).
- Vinorelbine is assumed to be administered at a dose of 25mg/m^2, when given either as monotherapy or part of combination therapy.
- Unused portions of vials of trastuzumab are assumed to be discarded within the base case analysis.
- The costs of oral therapies includes wastage for those patients who discontinue therapy before completing their last prescription for such therapy.
- Radiotherapy resource use and costs are the same irrespective of treatment regimen.
- The use of special interventions (e.g. blood transfusions) and their costs are the same irrespective of treatment regimen.
- End-of-life resource use and costs are independent of treatment (and time spent in each of the model states) and have thus been excluded from the modelling analysis (as these would be cancelled out for each comparison).
- Cardiac monitoring is undertaken every 3 months for patients receiving trastuzumab. The model assumes that patients receiving lapatinib plus capecitabine will be monitored according to the same schedule as patients receiving trastuzumab-containing regimens.
- The use of subsequent-line and salvage chemotherapies is not dependent on the use of prior therapy. Additional costs associated with such therapies are excluded from the analysis.

6.2.6.2. Why was this particular type of model used?

State transition models are commonly used to estimate the incremental cost-effectiveness of treatments for metastatic cancer. The approach adopted within this submission is similar to such an approach, as the model estimates the mean duration of time spent without disease progression and the mean duration of time spent following disease progression.

6.2.6.3. What was the justification for the chosen structure?

How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The use of a model structure based on progression-free and post-progression health states was selected as this is consistent with the clinical outcomes used within oncology trials, specifically study EGF100151. As patients typically remain on treatment until their disease progresses, there are clear cost differences for pre- and post-progression health states. In addition, whilst a number of different factors may influence a patient's health-related quality of life, evidence suggests that the presence of disease progression is a key determinant of health utility (Lloyd 2006; Earle 2000). The use of Weibull survival modelling to estimate the mean durations of progression-free survival and overall survival assumes that the hazard of experiencing either disease progression or death is time-dependent. As the model uses empirical Kaplan-Meier data on progression-free survival and overall survival, the duration of time spent in the post-progression health state is calculated as the difference between these health states.

The model explicitly estimates the mean duration spent in discrete health states over time. As noted above, the use of the Markov methodology is problematic as the progression-free Kaplan-Meier survival curves describe the probability of remaining progression-free at each point in time, and overall survival Kaplan-Meier curves

describe the probability of remaining alive at each point in time. These data do not allow for the direct calculation of transitions between pre-progression, post-progression and dead health states (e.g. a patient who is no longer progression-free may have progressed or died, patients who die may or may not have progressed beforehand). The approach adopted within this health economic analysis does not require such assumptions and is thus intuitively more sensible than the standard Markov approach. As progression-free survival and overall survival outcomes are likely to be correlated, bootstrapping techniques were used to estimate progression-free survival and overall survival outcomes within the probabilistic sensitivity analysis.

A discrete event simulation (DES) patient-level approach could have been used to evaluate the incremental cost-effectiveness of lapatinib plus capecitabine. However, similar assumptions concerning long-term outcomes for patients whose within-trial outcomes were censored would still have been required. Consequently, the use of a patient-level approach is unlikely to have added any precision to the methodology adopted within this health economic analysis; hence the DES approach was rejected.

6.2.6.4. What were the sources of information used to develop and inform the structure of the model?

The structure of the model and the methodology used to evaluate the cost-effectiveness of lapatinib plus capecitabine was based closely on the approach employed by Tappenden et al within a prior NICE assessment (Tappenden 2006a). The structure of the model was further developed through consultation with a number of health economists and clinical experts.

6.2.6.5. Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The model captures the key costs and health outcomes associated with the treatment of HER-2 positive metastatic breast cancer. Owing to a paucity of evidence concerning the impact of the range of adverse events associated with alternative chemotherapies for metastatic breast cancer, these costs are assumed to be the same for all treatment regimens within the base case analysis (although differential costs associated with adverse events are explored within the sensitivity analysis presented in Section 6.3.3.). For the same reason, the base case analysis does not include treatment-specific utility decrements for the incidence of adverse events. The potential impact of differential utilities for infusional and oral regimens is explored within the sensitivity analysis (see Section 6.3.3).

6.2.6.6. For discrete time models, what was the model's cycle length, and why was this length chosen?

Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

Kaplan-Meier estimates were evaluated on a 1-day basis to ensure precision of the resulting time-to-event estimates for use in the survival model. Whilst the model does not use a Markov approach as such, the cycle length is effectively 1-day in duration.

6.2.6.7. Was a half-cycle correction used in the model? If not, why not?

A half-cycle correction was not used within the model. However, as the model estimates mean time in the pre- and post-progression health states in daily increments, the inclusion of a half-cycle correction is neither warranted nor necessary.

6.2.6.8. Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)?

If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Yes. Weibull survival modelling has been used to extrapolate health outcomes for those patients receiving lapatinib plus capecitabine and for those patients receiving capecitabine monotherapy. Weibull survival distributions (see Section 6.2.6.1) have been estimated using regression methods to fit curves to empirical time-to-event data on progression-free survival and overall survival within study EGF100151. An assumption of proportional hazards between events within the lapatinib plus capecitabine and capecitabine monotherapy groups is assumed within the base case analysis. Figures 6.5 and 6.6 show the empirical and modelled time-to-event data assuming proportional hazards; the figures clearly show a good fit to the empirical Kaplan-Meier survival data for the lapatinib plus capecitabine group within study EGF100151.

As noted in Section 6.2.6.1, there is no direct evidence to demonstrate the relative clinical benefits of lapatinib plus capecitabine as compared to trastuzumab-containing regimens or vinorelbine monotherapy. For the former comparison, a pooled estimate of the hazard ratio has been estimated to describe progression-free survival durations for trastuzumab-containing regimens as compared to lapatinib plus capecitabine. Post-progression survival for patients receiving trastuzumab is assumed to be the same as for the lapatinib plus capecitabine group.

Similarly, there is not direct evidence to demonstrate the relative clinical benefits of lapatinib plus capecitabine as compared to vinorelbine monotherapy. Within the analysis, the model assumes that vinorelbine is of equal effectiveness to capecitabine monotherapy.

b) Non-model-based economic evaluations

6.2.6.9. Was the evaluation based on patient-level economic data from a clinical trial or trials?

The analysis takes the form of a mathematical model rather than a trial-based economic evaluation, and as such sections 6.2.6.9 to 6.2.6.13 are not applicable.

6.2.6.10. Provide details of the clinical trial, including the rationale for its selection.

6.2.6.11. Were data complete for all patients included in the trial?

If not, what were the methods employed for dealing with missing data for costs and health outcomes?

6.2.6.12. Were all relevant economic data collected for all patients in the trial?

If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

6.2.6.13. Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)?

If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

6.2.7. Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

6.2.7.1. How was the baseline risk of disease progression estimated?

***Also state which treatment strategy represents the baseline*.**

The baseline risk of disease progression for patients receiving capecitabine monotherapy was estimated by fitting a Weibull survival curve to the empirical patient-level progression-free survival data from study EGF100151, which are discussed in detail in Section 5.4. Details of the methods used to undertake this form of regression modelling are presented in Section 6.2.6. The risk of progression for patients receiving vinorelbine monotherapy is assumed to be equivalent to the risk for the capecitabine monotherapy group observed within study EGF100151 (NICE TA no. 62). The risk of disease progression for lapatinib plus capecitabine and trastuzumab-containing regimens was modelled using relative hazard ratios. The capecitabine treatment strategy represents the baseline as all other strategies were modelled via this data.

6.2.7.2. Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])?

If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Yes. The number of QALYs gained is estimated through a 2-stage process. Firstly, the model estimates the mean duration of time spent in the progression-free and post-progression health states. Utility scores are assumed to differ according to the patient's disease status (i.e. whether they have experienced disease progression or not). The duration of time spent in each state is then weighted by the utility score assigned to the appropriate health state.

The model differentiates the level of health-related quality of life (HRQoL) associated with the presence or absence of disease progression based on direct EQ-5D utility estimates from study EGF100151 and a utility study reported by Lloyd et al (Lloyd 2006). The mean duration of time spent in each health state is dependent on the treatment regimen under consideration.

Survival data for lapatinib plus capecitabine and capecitabine monotherapy were modelled from the EGF100151 trial data (03 April 2006 cut-off) and vinorelbine efficacy was assumed to equal that of capecitabine. Survival data were not available for patients receiving trastuzumab-containing regimens. Overall survival of patients within these treatment groups was calculated by estimating the duration spent without disease progression (relative to the lapatinib plus capecitabine group) and assuming that post-progression survival is equivalent to the lapatinib plus capecitabine group. In this sense, progression-free survival outcomes are assumed to translate directly into overall survival outcomes for patients receiving trastuzumab-containing regimens.

The relationship between disease progression endpoints and overall survival (OS) has been demonstrated in other cancers (Johnson K 2006; Sargent 2005). More recently improvements in TTP and PFS have been shown to correlate with increases in overall survival in metastatic breast cancer (Sherrill 2007, RTI Health Solutions report for GSK, data on file), as discussed in Section 5.3.4.1.

6.2.7.3. Were the health effects of adverse effects associated with the technology included in the economic evaluation?

If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

Within the base case analysis, pre-progression utility scores for lapatinib plus capecitabine and capecitabine monotherapy were derived directly from study EGF100151, and since there was no difference in utility between the two arms the data were pooled to derive a pre-progression utility value. Therefore for this specific comparison the impact of adverse events on HRQoL is accounted for within the utility data, and as it is essentially identical for both treatment arms will therefore have no impact on the cost-effectiveness of lapatinib in this scenario. For the vinorelbine and trastuzumab regimen comparisons the model does not specifically include the differential impact of treatment-specific adverse events on a patient's HRQoL. A considerable number of assumptions would be required to incorporate the HRQoL impact of these within the model (specifically in terms of the independence and the duration of events), and for this reason this was also excluded from the base case analysis in these scenarios. If it had been feasible to include these health effects, it is difficult to predict with any certainty what the impact on the cost-effectiveness of lapatinib plus capecitabine would be. However, data from EGF100151 show that lapatinib plus capecitabine is a well tolerated regimen with a manageable toxicity profile, and there is no reason to believe that the incorporation of the impact of adverse effects in the indirect comparisons would have a material effect on cost-effectiveness, in the context of the decision problem.

The potentially differential impact of infusional and oral regimens on health utility is explored within the sensitivity analysis presented in Section 6.3.3.

6.2.7.4. Was expert opinion used to estimate any clinical parameters?

If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Expert opinion was not used to inform any of the clinical parameter values assumed within the model.

6.2.7.5. What remaining assumptions regarding clinical evidence were made?

Why are they considered to be reasonable?

The model assumes that the hazard of experiencing disease progression or death is time-dependent. The model also assumes that the event hazard rate in the lapatinib plus capecitabine treatment group is proportional to the event hazard rate within the capecitabine monotherapy treatment group.

Survival data were not available for patients receiving relevant trastuzumab-containing regimens (monotherapy, plus capecitabine, plus vinorelbine). Overall survival of patients within these treatment groups was calculated by estimating the duration spent without disease progression (relative to the lapatinib plus capecitabine group) and assuming that post-progression is equivalent to the lapatinib plus capecitabine group. Progression-free survival outcomes are therefore assumed to translate directly into overall survival outcomes for these patients.

These assumptions are described in detail in Section 6.2.6.1.

6.2.8. Measurement and valuation of health effects

6.2.8.1. Which health effects were measured and how was this undertaken?

Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

The model estimates progression-free survival, post-progression survival, life years gained, and QALYs gained. The base case model does not include estimates of regimen-specific adverse events or their impact upon health-related quality of life. Progression-free survival and overall survival were measured for the lapatinib plus capecitabine and capecitabine monotherapy groups directly within study EGF100151. Progression-free survival outcomes for patients receiving trastuzumab-containing regimens were estimated using a pooled analysis of TTP from non-randomised studies (see Section 5.4). Progression-free survival and overall survival outcomes for patients receiving vinorelbine were assumed to be equivalent to those for patients receiving capecitabine monotherapy observed within study EGF100151.

Post-progression survival was estimated as the difference between overall survival and progression-free survival durations within each treatment group for the comparisons of lapatinib plus capecitabine versus capecitabine and vinorelbine monotherapies. However, for comparisons of lapatinib plus capecitabine versus trastuzumab-containing therapies, post-progression survival for trastuzumab-containing therapies was assumed to equal that of lapatinib plus capecitabine (see Section 6.2.6). QALYs were estimated by applying state-specific utilities to the mean duration spent in each health state for each of the six included treatment groups.

6.2.8.2. Which health effects were valued?

If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?

The number of QALYs gained within each treatment group are based on differences in the mean duration of time spent prior to and following disease progression. The pre-progression utility score (utility=0.69) was derived from a within-trial EQ-5D assessment of patients across the two treatment groups using the EQ-5D health questionnaire, valued using the tariffs reported by Dolan et al (Dolan 1997). The estimated utility score for the post-progression health state (utility=0.47) derived from Lloyd et al (Lloyd 2006), relates to UK societal preferences elicited using the standard gamble technique. Further details of the measurement and valuation of health effects is presented in Section 6.2.6.1.

A systematic literature search was not undertaken to select these values. However, they are thought to be appropriate for this disease setting and these values have also been tested in sensitivity analyses reported in Section 3.3.3.

6.2.8.3. Were health effects measured and valued in a manner that was consistent with NICE's reference case?

If not, which approach was used?

The methods used to measure and value health effects for the model's health states are in line with NICE's Reference Case.

6.2.8.4. Were any health effects excluded from the analysis? If so, why were they excluded?

Each of the treatment regimens included in the model are associated with adverse events which may negatively impact upon a patient's health-related quality of life. Utility decrements relating to specific adverse events were not available from the

EGF100151 trial, and are only partially available from the literature (see Section 6.2.7.3). The inclusion of such effects would require numerous assumptions concerning the durations for which the patient experiences adverse events, and the independence or interdependence of events. Further assumptions would be required concerning the multiplicative or additive impact of such events. These events are already captured for lapatinib plus capecitabine and capecitabine monotherapy in the pre-progression utility estimate; further inclusion would therefore lead to a downward biasing of resulting utility estimates due to double counting. For the trastuzumab-containing regimens and vinorelbine monotherapy, the inclusion of adverse events would require further assumptions based on indirect clinical comparisons and extremely limited adverse event data in this disease setting. Consequently, disutilities associated with adverse events are not included in the base case analysis.

6.2.8.5. If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

The primary health economic outcome used within the analysis was the incremental cost per QALY gained.

6.2.9. Resource identification, measurement and valuation

6.2.9.1. What resources were included in the evaluation?
(The list should be comprehensive and as disaggregated as possible.)

Nine groups of resource and cost components are included in the health economic model. These include drug acquisition, hospital resources for chemotherapy administration, pharmacy preparation and dispensing, resources to manage adverse events, diagnostic and laboratory tests, clinical consultation, radiotherapy resources, other special interventions and monitoring. These are described in detail in Section 6.2.6.

6.2.9.2. How were the resources measured?

Resource use was not measured directly within the EGF100151 trial. Drug usage data were estimated including adjustments for both missed doses and wastage. Assumptions concerning weekly hospital attendances for infusional treatment regimens (i.e. trastuzumab-containing regimens and vinorelbine) were based upon recommendations for current practice in England and Wales, where permitting. (NICE TA no. 107). Pharmacy resource requirements for each regimen were based on two previous NICE health technology assessment reports of treatments for metastatic colorectal cancer (Tappenden 2006a; Hind 2005). Assumptions concerning monitoring schedules for adverse events for patients receiving lapatinib or trastuzumab were derived from the trastuzumab NICE ERG report (Ward 2006). All other resources were measured within a study of the costs of managing metastatic breast cancer reported by Remak et al (Remak 2004).

6.2.9.3. Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Efficacy data for the lapatinib plus capecitabine and capecitabine regimens were obtained from the EGF100151 trial. Drug usage for lapatinib and capecitabine were derived using outcomes data collected within this study. As relative dose intensity (RDI) data were not collected during the studies used to estimate efficacy for trastuzumab- containing regimens, RDI estimates from EGF100151 were assumed to also reflect RDI for trastuzumab-containing regimens and vinorelbine monotherapy

(see Section 6.2.6.1, Drug acquisition costs). Other resources were measured using alternative external sources as above.

6.2.9.4. Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)?

Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

As far as the available evidence would allow, all relevant resources were included for the entire time horizon.

The only omission from the model which is likely to result in differences relates to the costs associated with managing adverse events due to specific treatment regimens. This exclusion from the base case was due to a lack of data. However, this issue has been partially addressed within the sensitivity analysis presented in Section 6.3.3.

Costs associated with any subsequent-line or salvage chemotherapies and end-stage disease are not explicitly included in the cost-effectiveness model as there is no evidence to suggest that resource use would be different between the treatment groups included in the model. Sensitivity analyses have been conducted to address the effects of varying the total costs (see Section 6.3.3).

6.2.9.5. What source(s) of information were used to value the resources?

Drug acquisition costs were obtained from the BNF (BNF No. 52 2006), and from the manufacturers of lapatinib and vinorelbine. NHS Reference Costs 2006 were used to value the cost of hospital attendances for chemotherapy. An earlier ERG report was used to value the cost of monitoring of patients receiving lapatinib and trastuzumab. (Ward 2006). Pharmacy costs were obtained from data provided by the NHS Christie Trust, as reported in two previous NICE assessment reports (Tappenden 2006a; Hind 2005). All other resources were valued using data reported within the study reported by Remak et (Remak 2004) (see Section 6.2.1).

6.2.9.6. What is the unit cost (excluding VAT) of the intervention(s) included in the analysis?

Does this differ from the (anticipated) acquisition cost reported in section 1?

Unit costs of drug acquisition for each regimen component included in the economic analysis are presented in Table 6.6. Sensitivity analyses have been carried out on the likely range of lapatinib prices (see Section 6.3.3).

6.2.9.7. Were the resources measured and valued in a manner consistent with the reference case?

If not, how and why do the approaches differ?

Yes. All resources were valued according to NICE Reference Case.

6.2.9.8. Were resource values indexed to the current price year?

All costs are valued at 2006 prices. Where 2006 prices were not available, these have been uplifted using the Hospital and Community Services Prices Index (Curtis 2006).

6.2.9.9. Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

A detailed list of assumptions concerning the measurement and valuation of resources is presented in Section 6.2.6.1.

6.2.10. Time preferences. Were costs and health benefits discounted at the rates specified in NICE's reference case?

Yes. Costs and health outcomes were discounted at a rate of 3.5% per year.

6.2.11. Sensitivity analysis

Sensitivity analysis should be used to deal with sources of main uncertainty other than that related to the precision of the parameter estimates.
For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.2.11.1. Which variables were subject to sensitivity analysis?

How were they varied and what was the rationale for this?

Simple sensitivity analysis was undertaken to explore the impact of changing assumptions concerning key model parameter values on the incremental cost-effectiveness of lapatinib plus capecitabine. This analysis was comprehensive and included a detailed examination of assumptions concerning the chemotherapy resources, health state costs and utilities, clinical benefits for treatment regimens not evaluated within study EGF100151, the survival modelling methodology and discount rates. The methods used to perform these sensitivity analyses within the model, and the justification for their inclusion, are presented below.

- Scenarios 1 and 2. The impact of assuming lower and higher prices for lapatinib on its cost-effectiveness was explored. Prices of £10.45 and £11.60 per lapatinib tablet were assumed.
- Scenario 3. The impact of varying the dosage of capecitabine when used alongside trastuzumab was explored due to uncertainty surrounding current use of this regimen in England and Wales. The impact of assuming a dose of 2000mg/m2 was explored within the sensitivity analysis.
- Scenario 4: There is uncertainty surrounding the dose intensity (RDI) parameters used within the model, particularly those relating to trastuzumab-containing regimens and vinorelbine monotherapy. For this reason, the impact of assuming perfect dose intensity was explored by setting all RDI parameters equal to 100%.
- Scenario 5: There is uncertainty surrounding the impact of wastage of all therapy regimens on the incremental cost-effectiveness of lapatinib plus capecitabine. The impact of excluding all wastage of all therapy regimens on cost-effectiveness was explored.
- Scenario 6: There is uncertainty concerning whether patients who continue to receive trastuzumab following disease progression receive an initial loading dose. The assumption that 100% of patients receive an initial loading dose of 4mg/kg was explored within the sensitivity analysis.
- Scenarios 7 and 8: There is uncertainty concerning the duration and frequency of use of vinorelbine-containing regimens. The sensitivity analysis explored the impact of assuming that patients receive vinorelbine treatment on days 1 and 8 of a 21-day cycle, and that all patients receiving vinorelbine stop therapy with this drug after 6 cycles.
- Scenario 9: A sensitivity analysis was undertaken whereby trastuzumab is assumed to be given at 6mg/kg every 3 weeks.
- Scenario 10: A further sensitivity analysis was undertaken whereby trastuzumab was assumed to be given at 6mg/kg every 3 weeks, whilst vinorelbine was assumed to be given on days 1 and 8 of a 21-day cycle for a maximum of 6 cycles (a combination of scenarios 7, 8 and 9 together).
- Scenarios 11 and 12: Owing to a lack of direct evidence, there is considerable uncertainty surrounding the relative benefit of lapatinib plus capecitabine as

compared against trastuzumab-containing regimens. Two alternative scenarios were explored: the first assumed that the progression-free survival duration for trastuzumab-containing regimens is equal to that for capecitabine monotherapy in EGF100151 whilst the second assumed that the progression-free survival duration for trastuzumab-containing regimens is equal to that for lapatinib plus capecitabine.

- Scenario 13: The impact of assuming independent- rather than proportional hazards in event rates between treatment groups was explored.
- Scenario 14: The use of investigator-assessed progression-free outcomes was explored. This was undertaken using a separate statistical analysis of time-to-event data from study EGF100151, including an adjustment of the RDI parameters.
- Scenarios 15 and 16: The EGF100151 study did not collect sufficient information to allow for the calculation of a robust utility score for those patients following disease progression. Within the base case, the relative reduction in utility for post-progression versus pre-progression was based on a study reported by Lloyd (Lloyd 2006). In scenario 15 it is assumed that progression causes no decrease in utility. In scenario 16 an alternative scenario was explored whereby utility scores for pre-progression and post-progression health states were taken directly from Lloyd et al (Lloyd 2006); these scores were assumed to be 0.715 for the pre-progression health state and 0.715-0.272 (=0.443) for the post-progression health state.
- Scenario 17: There is some, albeit indirect, evidence which suggests that oral therapies may confer some additional benefits as compared against infusional breast cancer regimens (De Cock 2005). A non-systematic search of Medline identified one study which reported utilities for patients with breast cancer receiving infusional or oral therapies (De Cock 2005). This study suggested a difference in utility of 0.02. This value of 0.02 was applied as a decrement to the pre-progression therapy state for the infusional regimens within the sensitivity analysis.
- Scenario 18: The base case analysis does not include differential costs of adverse events specifically related to each therapy regimen. A simple sensitivity analysis was undertaken in which the incidence of the six most common adverse events and LVEF were analysed by treatment group within study EGF100151 to estimate the additional cost of managing adverse events for the lapatinib plus capecitabine groups. These adverse events included diarrhoea, PPE syndrome, nausea, vomiting, fatigue, rash and LVEF. Management strategies were assumed according to the grade of severity of each event based on the NCI CTCAE criteria. The management strategies for each adverse event were costed using NHS Reference Costs 2006, BNF No. 52 2006, and NICE technology assessment reports (Jones 2002; Forbes 2001; Ward 2006). For lapatinib plus capecitabine versus capecitabine monotherapy and trastuzumab plus capecitabine, an estimated difference in adverse event management costs between the EGF100151 study groups was assumed; this was calculated to be +£320 for patients receiving lapatinib. For the remaining comparisons, a higher expected cost equal to the absolute cost of managing adverse events in the lapatinib group was assumed; this was estimated to be £1,428 for patients receiving lapatinib, and represents a very conservative approach since the costs of treatment related adverse effects have not been included for these indirect comparators. Further details of this analysis are provided in Appendix 9.9.
  NB. This analysis cannot be run directly using the current version of the model and must be performed outside the model framework as above.

- Scenarios 19 and 20: There is uncertainty surrounding the resource requirements and costs associated with treating patients with metastatic breast cancer. Whilst the majority of health state costs were consistently sourced from the study reported by Remak et al (Remak 2004), the authors did not provide any standard errors around the mean cost estimates. Within the sensitivity analysis, the impact of varying all health state costs by +/-25% was explored.
- Scenarios 21 and 22: In line with NICE's Reference Case, the impact of discounting was explored within two scenarios: firstly the impact of no discounting was examined, and secondly, the impact of discounting costs and health effects at 6% and 1.5% respectively.

6.2.11.2. Was probabilistic sensitivity analysis (PSA) undertaken?

If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Yes, probabilistic sensitivity analysis was undertaken. Probability distributions were used to describe the uncertainty surrounding the mean values of all uncertain parameters within the model. The details of all uncertain probability distributions, means and standard errors are presented in Section 6.2.6.1. Non-parametric bootstrapping techniques were used to estimate correlated distributions for overall survival and progression-free survival outcomes. The probabilistic sensitivity analysis consisted of 2,000 random iterations for each incremental comparison. See Appendix 9.8 for a list of all variables used in the probabilistic sensitivity analysis.

6.2.11.3. Has the uncertainty associated with structural uncertainty been investigated?

To what extent could/does this type of uncertainty change the results?

The assumption of proportional hazards for the lapatinib plus capecitabine versus capecitabine monotherapy was explored within a structural sensitivity analysis (Scenario 13). The results of this analysis are presented in Section 6.3.3.

6.2.12. Statistical analysis

6.2.12.1. How were rates or probabilities based on intervals transformed into (transition) probabilities?

The model does not use transition probabilities. Patient-level time-to-event data on progression-free survival and overall survival were used to fit Weibull survival distributions (see Section 6.2.6.1).

6.2.12.2. Is there evidence that (transition) probabilities should vary over time for the condition or disease?

If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The model assumes that event hazard rates are time-dependent, hence Weibull distributions are used to model clinical outcomes. Figures 6.3 to 6.6 demonstrate that this assumption is appropriate, as the parametric survival models fit the empirical Kaplan-Meier data with a sufficient degree of precision (see Section 6.2.6.1 for further details).

6.2.13. Validity

Describe the measures that have been undertaken in order to validate and check the model.

As far as possible, the validity of the model has been addressed through consideration of Eddy's four levels of model validation (Eddy 1985). In addition, peer

review of the model and submission was conducted by two academic health economists.

First-order validation: Concurrence of clinical experts

The structure of the model uses time-to-event data and hazard ratios obtained directly from the EGF100151 clinical trial, and is based upon a model structure that has previously been used to evaluate the cost-effectiveness of treatments for metastatic colorectal cancer (Tappenden 2006a). As such, the model structure is intuitively sensible from a clinical perspective.

Second-order validation – internal concurrence

A review by an external health economics agency was commissioned to ensure the internal validity of the economic model in this de novo evaluation (the original model). The aim of the validation was to ensure that the model produces estimates of costs and effects corresponding to the model specification (report available on request, but summarised below).

Methods

1. A new version of the model (the validation model) was built in Excel according to the model specification in the original model user manual. The validation model was developed using cell formulae rather than visual basic code, with the exception of the probabilistic analysis macro, to improve transparency and aid validation.
2. An empirical validation was conducted by comparing the costs and effects as estimated by the validation model to the estimates obtained from the original model using the parameter set included in the original model and a number of alternative scenarios including plausible parameter values.
3. Further testing of the model was conducted using a range of extreme parameter values, and the structure, cell formulae and visual basic code was examined for programming errors.

Results

The cost and effect estimates produced by the original model were identical with the results obtained from the validation model based on the parameter set included in the original model and a number of alternative scenarios including plausible parameter values for costs and parameter values.

The models were tested using extreme parameter values for hazard ratios, Weibull parameters and costs. In each case the models functioned correctly and no error messages were detected when single parameters or multiple parameters were varied. A list of extreme values used is included in Appendix 9.10.

No errors were found when the structure, cell formulae and visual basic code were examined for potential programming errors.

Third- and fourth-level validation – ability to predict non-modelled data sources

As this economic analysis represents the first evaluation of the cost-effectiveness of lapatinib plus capecitabine for the treatment of women with HER2+ metastatic breast cancer following progression on trastuzumab, and is based primarily on a single clinical trial, there are no further sources of clinical evidence against which to validate the outcomes predicted by the model.

6.3. Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- ***costs, QALYs and incremental cost per QALY***
- ***disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment***
- ***a statement as to whether the results are based on a probabilistic sensitivity analysis***
- ***cost-effectiveness acceptability curves***
- ***scatterplots on cost-effectiveness quadrants.***

6.3.1. Base-case analysis

6.3.1.1. What were the results of the base-case analysis?

The central estimates of cost-effectiveness for lapatinib plus capecitabine versus capecitabine monotherapy, vinorelbine monotherapy, trastuzumab plus vinorelbine, trastuzumab plus capecitabine and trastuzumab monotherapy are presented in Tables 6.10 to 6.14 respectively. These estimates are based on a deterministic analysis of the model. Descriptions of the results below are restricted to tables, only, to avoid unnecessary use of space.

Please note that the incremental cost-effectiveness and cost-utility ratios in the tables below are derived directly from the modelled outputs, and due to rounding within the model may differ slightly from ratios calculated directly from the cost- and effectiveness outputs within the tables.

Comparison 1: Lapatinib plus capecitabine versus capecitabine monotherapy

Table 6.10 Central estimates of cost-effectiveness and cost-utility: lapatinib plus capecitabine versus capecitabine monotherapy (discounted)

	Lapatinib plus capecitabine	Capecitabine monotherapy	Incremental
Progression-free life years	0.694	0.426	0.268
Post-progression life years	0.794	0.826	-0.033
Life years	1.488	1.252	0.236
QALYs	0.857	0.686	0.171
Acquisition costs	£14,120	£2,168	£11,953
Administration costs	£227	£84	£144
Monitoring costs	£461	£0	£461
Treatment-specific adverse events costs	£0	£0	£0
Other progression-free costs	£4,122	£2,529	£1,593
Other post-progression costs	£6,747	£7,025	-£277
Total costs	£25,678	£11,805	£13,873
Cost per LYG	-	-	£58,880
Cost per PFLYG	-	-	£51,717
Cost per QALY gained	-	-	£81,251

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Comparison 2: Lapatinib plus capecitabine versus vinorelbine monotherapy

This analysis assumes that progression-free survival and overall survival outcomes for patients receiving vinorelbine are the same as the outcomes within the capecitabine monotherapy group evaluated within study EGF100151.

Table 6.11 Central estimates of cost-effectiveness and cost-utility: lapatinib plus capecitabine versus vinorelbine monotherapy (discounted)

	Lapatinib plus capecitabine	Vinorelbine monotherapy	Incremental
Progression-free life years	0.694	0.426	0.268
Post-progression life years	0.794	0.826	-0.033
Life years	1.488	1.252	0.236
QALYs	0.857	0.686	0.171
Acquisition costs	£14,120	£2,978	£11,143
Administration costs	£227	£1,562	-£1,335
Monitoring costs	£461	£0	£461
Treatment-specific adverse events costs	£0	£0	£0
Other progression-free costs	£4,122	£2,529	£1,593
Other post-progression costs	£6,747	£7,025	-£277
Total costs	£25,678	£14,094	£11,584
Cost per LYG	-	-	£49,166
Cost per PFLYG	-	-	£43,185
Cost per QALY gained	-	-	£67,847

Comparison 3: Lapatinib plus capecitabine versus trastuzumab plus vinorelbine

This analysis assumes that post-progression survival for the two treatment groups is equivalent, hence progression-free survival differences are assumed to translate directly into overall survival differences.

Table 6.12 Central estimates of cost-effectiveness and cost-utility: lapatinib plus capecitabine versus trastuzumab plus vinorelbine (discounted)

	Lapatinib plus capecitabine	Trastuzumab plus vinorelbine	Incremental
Progression-free life years	0.694	0.489	0.206
Post-progression life years	0.794	0.794	-
Life years	1.488	1.282	0.206
QALYs	0.857	0.714	0.143
Acquisition costs	£14,120	£13,691	£429
Administration costs	£227	£6,466	-£6,239
Monitoring costs	£461	£324	£137
Treatment-specific adverse events costs	£0	£0	£0
Other progression-free costs	£4,122	£2,901	£1,221
Other post-progression costs	£6,747	£6,747	£0
Total costs	£25,678	£30,131	-£4,452
Cost per LYG	-	-	Lapatinib plus capecitabine dominates

	Lapatinib plus capecitabine	Trastuzumab plus vinorelbine	Incremental
Cost per PFLYG	-	-	Lapatinib plus capecitabine dominates
Cost per QALY gained	-	-	Lapatinib plus capecitabine dominates

Comparison 4 : Lapatinib plus capecitabine versus trastuzumab plus capecitabine

As with comparison 3, this analysis assumes that post-progression survival for the two treatment groups is equivalent.

Table 6.13 Central estimates of cost-effectiveness and cost-utility: lapatinib plus capecitabine versus trastuzumab plus capecitabine (discounted)

	Lapatinib plus capecitabine	Trastuzumab plus capecitabine	Incremental
Progression-free life years	0.694	0.489	0.206
Post-progression life years	0.794	0.794	-
Life years	1.488	1.282	0.206
QALYs	0.857	0.714	0.143
Acquisition costs	£14,120	£12,813	£1,307
Administration costs	£227	£5,077	-£4,850
Monitoring costs	£461	£324	£137
Treatment-specific adverse events costs	£0	£0	£0
Other progression-free costs	£4,122	£2,901	£1,221
Other post-progression costs	£6,747	£6,747	£0
Total costs	£25,678	£27,864	-£2,186
Cost per LYG	-	-	Lapatinib plus capecitabine dominates
Cost per PFLYG	-	-	Lapatinib plus capecitabine dominates
Cost per QALY gained	-	-	Lapatinib plus capecitabine dominates

Comparison 5: Lapatinib plus capecitabine versus trastuzumab monotherapy

Again, this analysis assumes that post-progression survival for the two treatment groups is equivalent.

Table 6.14 Central estimates of cost-effectiveness and cost-utility: lapatinib plus capecitabine versus trastuzumab monotherapy (discounted)

	Lapatinib plus capecitabine	Trastuzumab monotherapy	Incremental
Progression-free life years	0.694	0.489	0.206
Post-progression life years	0.794	0.794	0.000
Life years	1.488	1.282	0.206
QALYs	0.857	0.714	0.143
Acquisition costs	£14,120	£10,906	£3,214
Administration costs	£227	£5,873	-£5,646

	Lapatinib plus capecitabine	Trastuzumab monotherapy	Incremental
Monitoring costs	£461	£324	£137
Treatment-specific adverse events costs	£0	£0	£0
Other progression-free costs	£4,122	£2,901	£1,221
Other post-progression costs	£6,747	£6,747	£0
Total costs	£25,678	£26,753	-£1,075
Cost per LYG	-	-	Lapatinib plus capecitabine dominates
Cost per PFLYG	-	-	Lapatinib plus capecitabine dominates
Cost per QALY gained	-	-	Lapatinib plus capecitabine dominates

Summary of central estimates of cost-effectiveness

Table 6.15 presents a summary of the central estimates of incremental cost-effectiveness for lapatinib plus capecitabine.

Table 6.15 Summary of central estimates of cost-effectiveness for lapatinib plus capecitabine

Incremental	Lapatinib plus capecitabine versus				
	Capecitabine monotherapy	Vinorelbine monotherapy	Trastuzumab plus vinorelbine	Trastuzumab plus capecitabine	Trastuzumab monotherapy
LYGs	0.236	0.236	0.206	0.206	0.206
QALYs	0.171	0.171	0.143	0.143	0.143
Cost	£13,873	£11,584	-£4,452	-£2,186	-£1,075
Cost per LYG	£58,880	£49,166	Lapatinib plus capecitabine dominates	Lapatinib plus capecitabine dominates	Lapatinib plus capecitabine dominates
Cost per QALY gained	£81,251	£67,847	Lapatinib plus capecitabine dominates	Lapatinib plus capecitabine dominates	Lapatinib plus capecitabine dominates

Probabilistic sensitivity analysis results

Comparison 1: Probabilistic sensitivity analysis results for lapatinib plus capecitabine versus capecitabine monotherapy

The results of the probabilistic sensitivity analysis for lapatinib plus capecitabine versus capecitabine are presented as a cost-effectiveness plane and cost-effectiveness acceptability curves in Figures 6.7 and 6.8 respectively.

Figure 6.7 Cost-effectiveness plane for lapatinib plus capecitabine versus capecitabine monotherapy

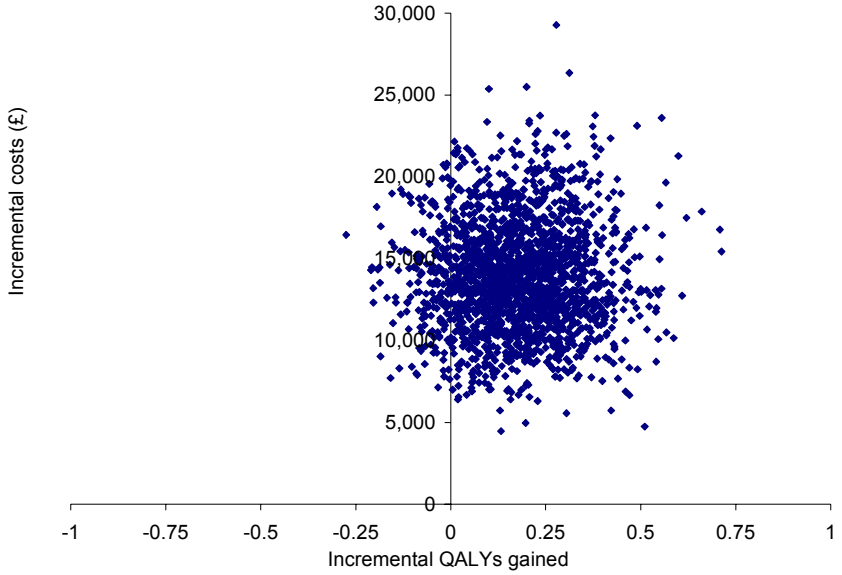
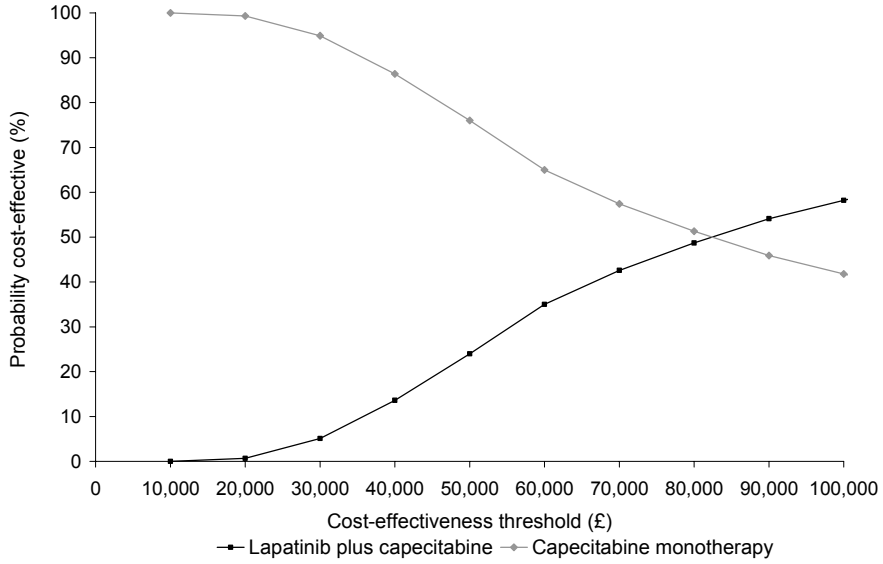


Figure 6.8 Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus capecitabine monotherapy



The cost-effectiveness plane shown in Figure 6.7 shows that the majority of sample estimates of the incremental costs and QALYs for lapatinib plus capecitabine fall in the North-East quadrant. In approximately 89.7% of simulations, lapatinib plus capecitabine is expected to produce more QALYs at a greater cost than capecitabine monotherapy. The CEAC shown in Figure 6.8 suggests that the probability that lapatinib plus capecitabine has an incremental cost-utility ratio that is better than £30,000 is approximately 0.05 when compared against capecitabine monotherapy. The probability that lapatinib plus capecitabine has an incremental cost-utility ratio that is better than £20,000 is approximately 0.01 when compared against capecitabine monotherapy. These results and those for further comparisons are summarised in Table 6.16.

Comparison 2: Probabilistic sensitivity analysis results for lapatinib plus capecitabine versus vinorelbine monotherapy (Figures 6.9 and 6.10).

Figure 6.9 Cost-effectiveness plane for lapatinib plus capecitabine versus vinorelbine monotherapy

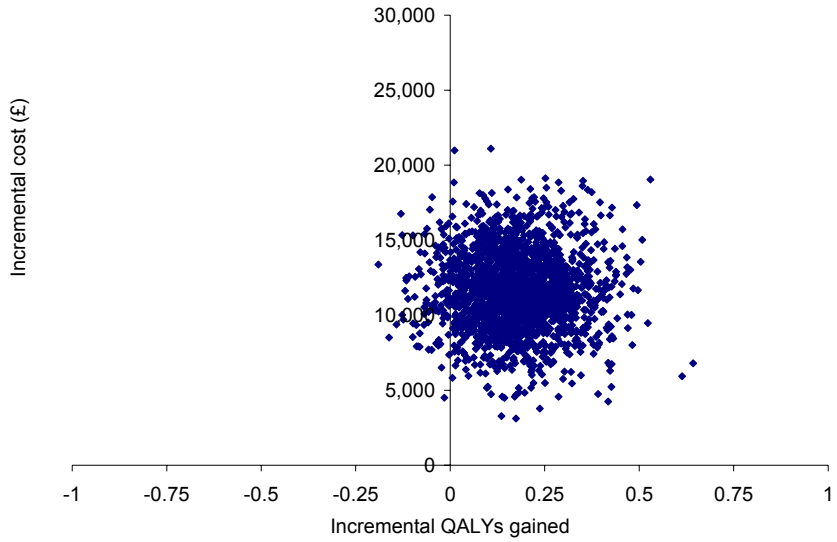
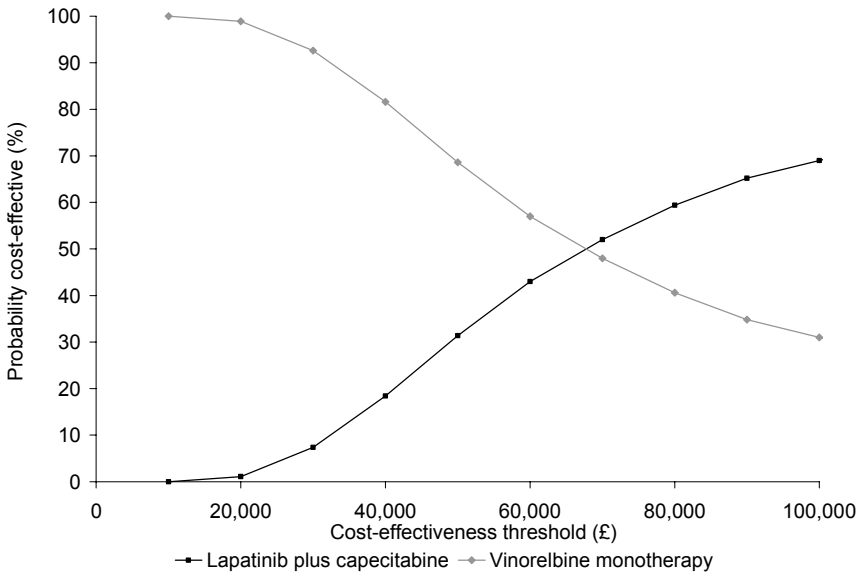


Figure 6.10 Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus vinorelbine monotherapy



Comparison 3: Probabilistic sensitivity analysis results for lapatinib plus capecitabine versus trastuzumab plus vinorelbine (Figures 6.11 and 6.12)

Figure 6.11 Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab plus vinorelbine

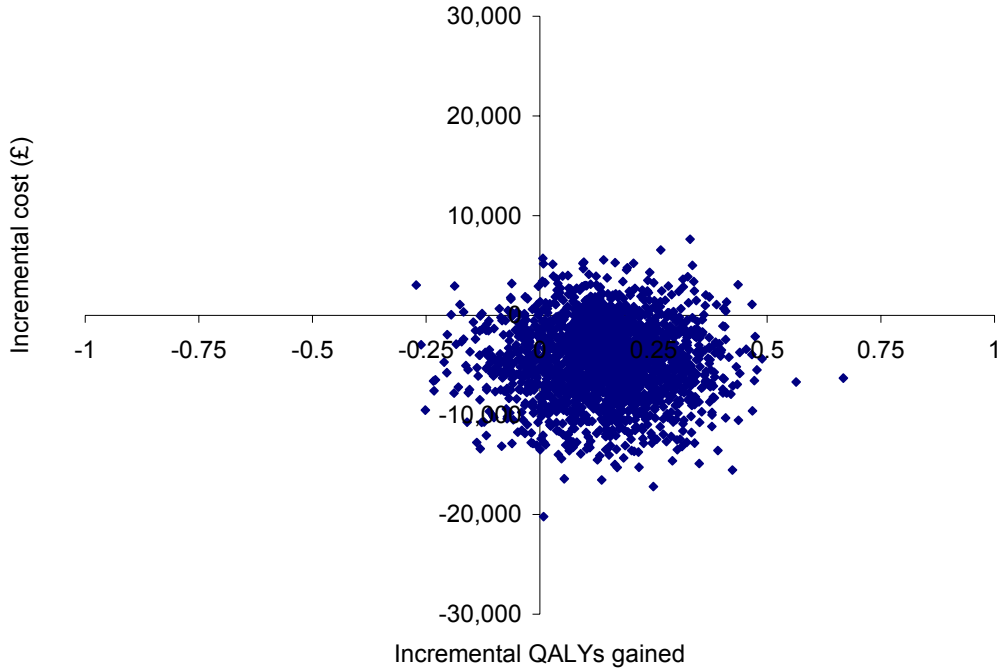
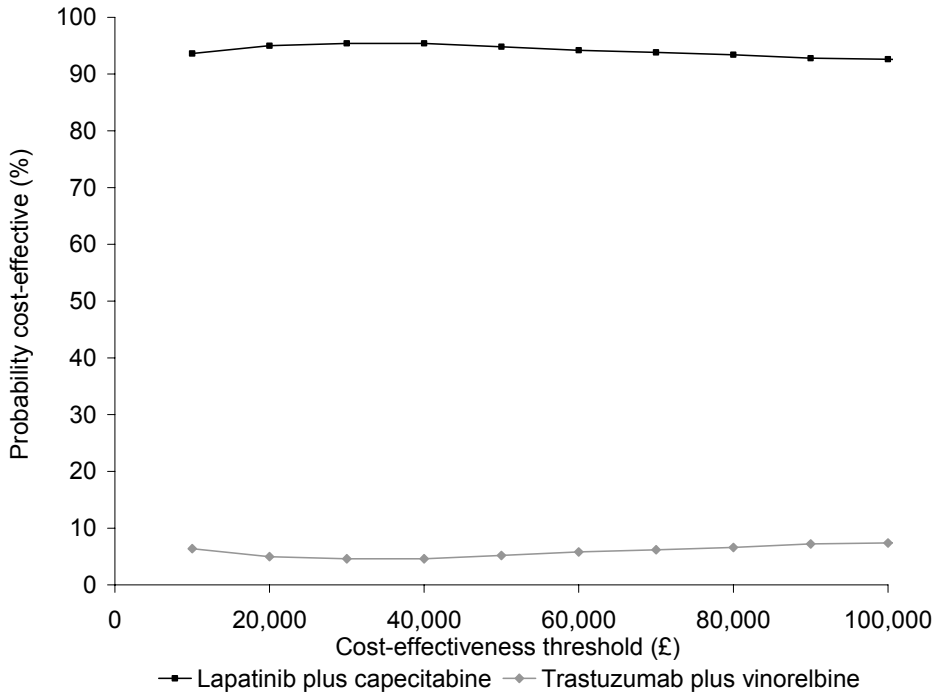


Figure 6.12 Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab plus vinorelbine



Comparison 4: Probabilistic sensitivity analysis results for lapatinib plus capecitabine versus trastuzumab plus capecitabine (Figures 6.13 and 6.14)

Figure 6.13 Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab plus capecitabine

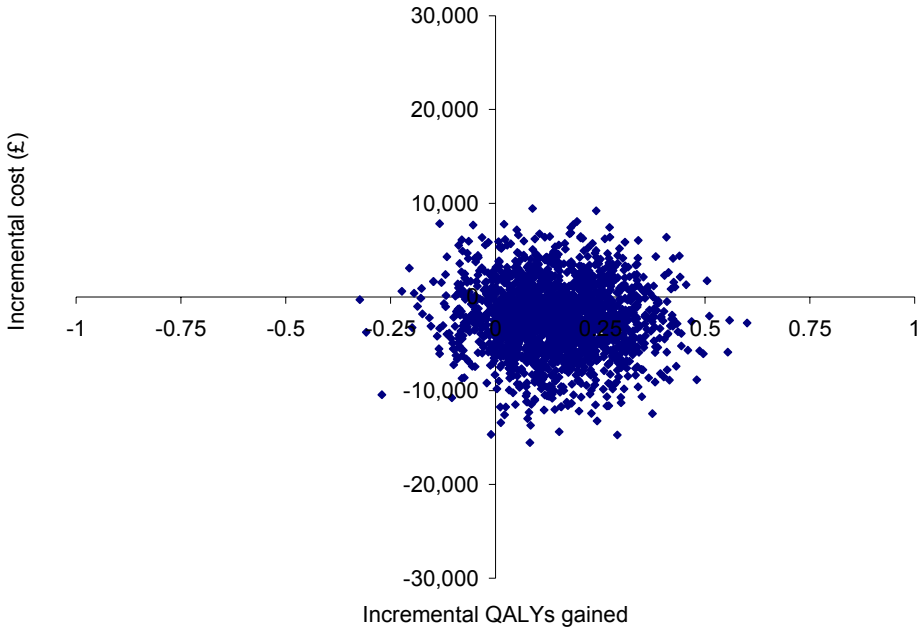
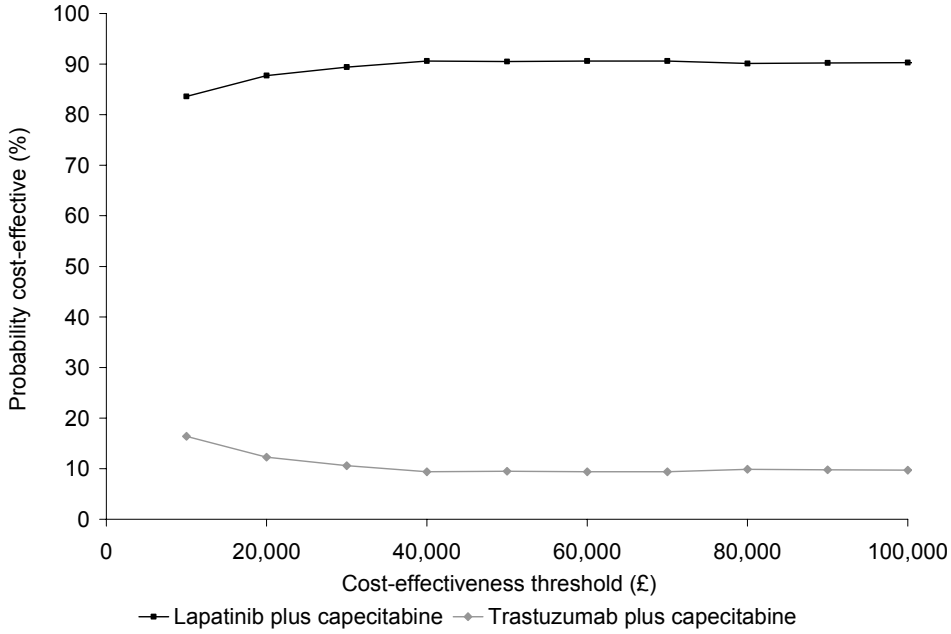


Figure 6.14 Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab plus capecitabine



Comparison 5: Probabilistic sensitivity analysis results for lapatinib plus capecitabine versus trastuzumab monotherapy (Figures 6.15 and 6.16)

Figure 6.15 Cost-effectiveness plane for lapatinib plus capecitabine versus trastuzumab monotherapy

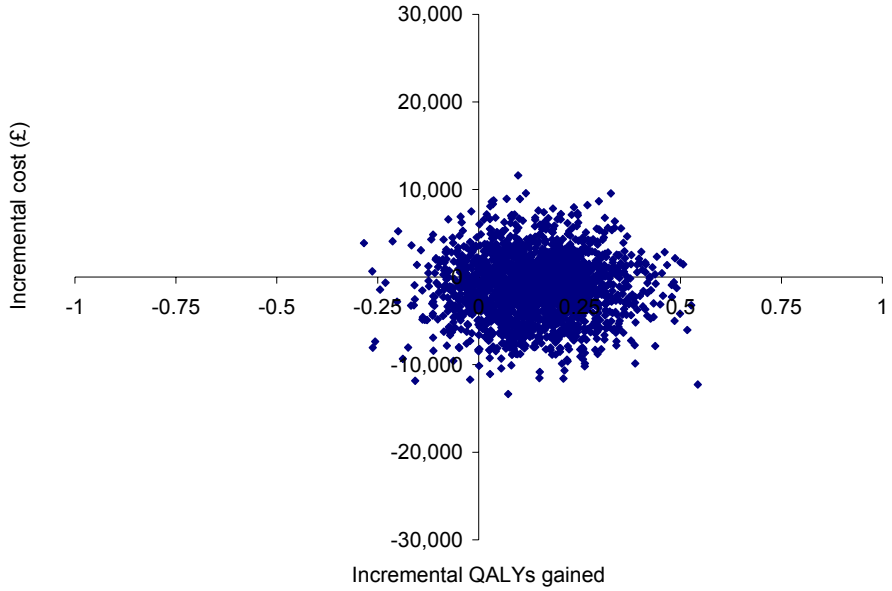


Figure 6.16 Cost-effectiveness acceptability curves for lapatinib plus capecitabine versus trastuzumab monotherapy

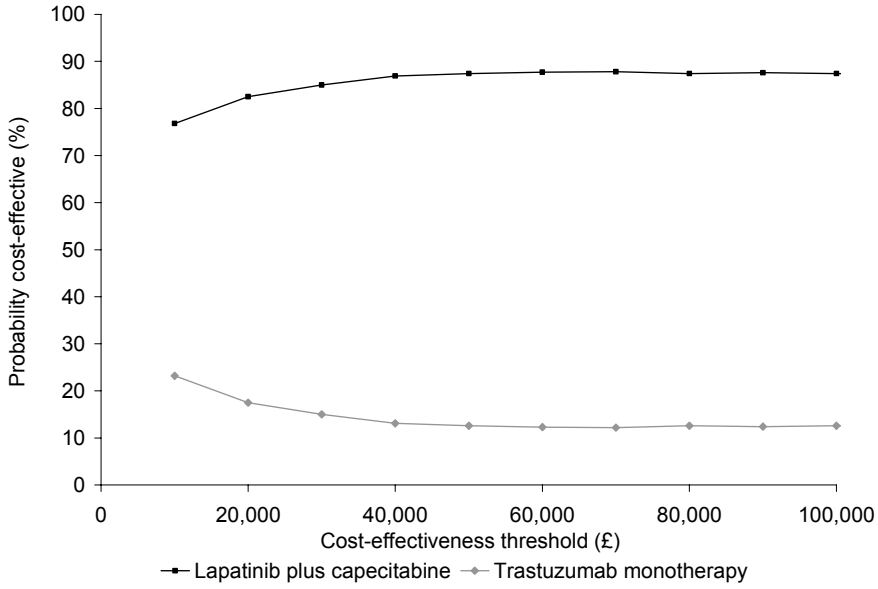


Table 6.16 Summary of probabilistic sensitivity analysis

	Lapatinib plus capecitabine versus				
PSA results	**Capecitabine monotherapy**	**Vinorelbine monotherapy**	**Trastuzumab plus vinorelbine**	**Trastuzumab plus capecitabine**	**Trastuzumab monotherapy**
Predominant quadrant	NE	NE	SE	SE	SE
% in predominant quadrant	89.7	94.6	78.3	66.6	55.1
Probability ICER <£20k	0.01	0.01	0.95	0.88	0.83
Probability ICER <£30k	0.05	0.07	0.95	0.89	0.85

6.3.2. Subgroup analysis

6.3.2.1. What were the results of the subgroup analysis/analyses if conducted?

Subgroup analyses were not undertaken within the health economic analysis.

6.3.3. Sensitivity analyses

6.3.3.1. What were the main findings of the sensitivity analyses?

Table 6.17 presents a summary of the results of the deterministic sensitivity analyses.

Table 6.17 Results of the deterministic sensitivity analyses

Scenario number - description	**Incremental cost per QALY gained for lapatinib plus capecitabine versus**				
	Capecitabine	**Vinorelbine**	**Trastuzumab plus vinorelbine**	**Trastuzumab plus capecitabine**	**Trastuzumab monotherapy**
Base case scenario	£81,251	£67,847	dominant (QALYs=+0.14, costs=-£4,452)	dominant (QALYs=+0.14, costs=-£2,186)	dominant (QALYs=+0.14, costs=-£1,075)
Scenario 1: Lapatinib price=£10.45 per tablet	£77,781	£64,377	dominant (QALYs=+0.14, costs=-£5,045)	dominant (QALYs=+0.14, costs=-£2,778)	dominant (QALYs=+0.14, costs=-£1,667)
Scenario 2: Lapatinib price=£11.60 per tablet	£85,036	£71,632	dominant (QALYs=+0.14, costs=-£3,806)	dominant (QALYs=+0.14, costs=-£1,539)	dominant (QALYs=+0.14, costs=-£429)
Scenario 3: 2,000mg/m^2 for capecitabine				dominant (QALYs=+0.14, costs=-£1,819)	
Scenario 4: RDI equals 100% for all medications	£101,576	£87,152	dominant (QALYs=+0.14, costs=-£6,158)	dominant (QALYs=+0.14, costs=-£3,149)	dominant (QALYs=+0.14, costs=-£273)
Scenario 5: Wastage excluded for all medications	£76,896	£65,887	dominant (QALYs=+0.14, costs=-£1,539)	£1,650	£6,772
Scenario 6: All patients receiving trastuzumab-containing regimens receive loading dose			dominant (QALYs=+0.14, costs=-£5,405)	dominant (QALYs=+0.14, costs=-£3,138)	dominant (QALYs=+0.14, costs=-£2,027)

Scenario number - description	Incremental cost per QALY gained for lapatinib plus capecitabine versus				
	Capecitabine	Vinorelbine	Trastuzumab plus vinorelbine	Trastuzumab plus capecitabine	Trastuzumab monotherapy
Scenario 7: Vinorelbine given on days 1 and 8 of a 21 day cycle		£77,647	dominant (QALYs=+0.14, costs=-£2,880)		
Scenario 8: Vinorelbine given as in scenario 7 but stopped after 6 cycles (18 weeks max)		£83,847	dominant (QALYs=+0.14, costs=-£1,731)		
Scenario 9: 3-weekly (6mg/kg) rather than 1-weekly (2mg/kg) trastuzumab regimen			£4,361	£20,248	£27,532
Scenario 10: Scenarios 7,8 and 9 together			£23,432		
Scenario 11: PFS for trastuzumab-containing regimens =PFS for capecitabine			dominant (QALYs=+0.17, costs=-£1,733)	£1,428	£7,099
Scenario 12: PFS for trastuzumab-containing regimens =PFS for lapatinib plus capecitabine			dominant (QALYs=0, costs=-£14,291)	dominant (QALYs=0, costs=-£11,070)	dominant (QALYs=0, costs=-£9,492)
Scenario 13: Independent hazards model rather than proportional hazards model	£154,564	£124,999	dominant (QALYs=0, costs=-£14,009)	dominant (QALYs=0, costs=-£10,848)	dominant (QALYs=0, costs=-£9,298)
Scenario 14: Investigator-assessed PFS	£95,766	£79,921	dominant (QALYs=+0.07, costs=-£8,797)	dominant (QALYs=+0.07, costs=-£6,121)	dominant (QALYs=+0.07, costs=-£2,045)
Scenario 15: Post-progression utility reduction =0% (i.e. utility =0.69 for pre- and post-progression states)	£84,841	£70,845	dominant (QALYs=+0.14, costs=-£4,452)	dominant (QALYs=+0.14, costs=-£2,186)	dominant (QALYs=+0.14, costs=-£1,075)
Scenario 16: Lloyd utilities (Lloyd 2006) (pre-progression = 0.715, post-progression = 0.443)	£78,228	£65,322	dominant (QALYs=+0.15, costs=-£4,452)	dominant (QALYs=+0.15, costs=-£2,186)	dominant (QALYs=+0.15, costs=-£1,075)
Scenario 17: Disutility of -0.02 assumed for infusional regimens		£60,804	dominant (QALYs=+0.16, costs=-£4,452)	dominant (QALYs=+0.16, costs=-£2,186)	dominant (QALYs=+0.16, costs=-£1,075)

Scenario number - description	Incremental cost per QALY gained for lapatinib plus capecitabine versus				
	Capecitabine	Vinorelbine	Trastuzumab plus vinorelbine	Trastuzumab plus capecitabine	Trastuzumab monotherapy
Scenario 18: Inclusion of additional adverse event costs associated with lapatinib regimen	£83,003	£69,861	dominant (QALYs=+0.14, costs=-£3,024)	dominant (QALYs=+0.14, costs=-£1,866)	£2,470
Scenario 19: Health state costs +25%	£83,176	£69,773	dominant (QALYs=+0.14, costs=-£4,147)	dominant (QALYs=+0.14, costs=-£1,880)	dominant (QALYs=+0.14, costs=-£770)
Scenario 20: Health state costs -25%	£79,325	£65,921	dominant (QALYs=+0.14, costs=-£4,758)	dominant (QALYs=+0.14, costs=-£2,442)	dominant (QALYs=+0.14, costs=-£1,380)
Scenario 21: Undiscounted costs and effects	£78,912	£66,092	dominant (QALYs=+0.15, costs=-£4,404)	dominant (QALYs=+0.15, costs=-£2,108)	dominant (QALYs=+0.15, costs=-£983)
Scenario 22: Costs and outcomes discounted at 6% and 1.5% respectively	£77,332	£64,443	dominant (QALYs=+0.15, costs=-£4,483)	dominant (QALYs=+0.15, costs=-£2,237)	dominant (QALYs=+0.15, costs=-£1,136)

The results shown in Table 6.16 suggest that the incremental cost-effectiveness of lapatinib plus capecitabine is stable to changes in most of the model parameters. Within the sensitivity analysis, the incremental cost-effectiveness of lapatinib plus capecitabine versus capecitabine monotherapy ranged from approximately £76,900 to £154,600 per QALY gained. The key determinants of cost-effectiveness for this comparison concern the dose intensity parameters and assumptions concerning the proportionality of event hazard rates.

Within the sensitivity analysis, the incremental cost-effectiveness of lapatinib plus capecitabine versus vinorelbine monotherapy ranged from £60,800 to £125,000 per QALY gained. The key determinants of cost-effectiveness for this comparison are the same as those for capecitabine and, in addition, assumptions concerning treatment duration for vinorelbine.

Within the sensitivity analysis, lapatinib plus capecitabine dominated the trastuzumab-containing regimens in the majority of scenarios (i.e. lapatinib plus capecitabine was more effective and less costly). Incremental cost effectiveness ratios (ICERs) ranged from dominating to approximately £27,500 per QALY gained. The key determinants of cost-effectiveness for these comparisons include the use of a 3-weekly trastuzumab regimen and assumptions concerning the frequency and duration of vinorelbine, which result in less favourable cost-effectiveness estimates for lapatinib plus capecitabine.

6.3.4. Interpretation of economic evidence

Lapatinib plus capecitabine provides superior outcomes in terms of progression-free life years, life years and QALYs versus single agent chemotherapies. This comparison is unlikely to meet thresholds for cost-effectiveness laid out in NICE's methodological guidance. However, for patients who would otherwise be treated with trastuzumab-containing therapies, the sensitivity analyses show that use lapatinib plus capecitabine is either a dominant or cost-effective option.

In the comparisons of lapatinib plus capecitabine versus trastuzumab-containing therapy, all the sensitivity analyses resulted in dominance or ICERs below

£30,000/QALY and in only 2 out of the 18 scenarios were the ICERs above £20,000/QALY. When 3-weekly trastuzumab dosing was assumed, the ICER for lapatinib plus capecitabine rose to £20,248 versus trastuzumab plus capecitabine and £27,532 versus trastuzumab monotherapy. The ICER versus trastuzumab plus vinorelbine only rose above £20,000/QALY (to £23,432/QALY) when additional changes to the vinorelbine dosing were also assumed. UK clinical practice varies between oncologists and may depend on patient characteristics. It is therefore likely that all the dosing scenarios explored in the sensitivity analysis occur to some extent in practice, despite the weekly dosing specified in the SmPC for trastuzumab use in the metastatic setting.

In line with Principle 4 of NICE's Social Value Judgments (NICE 2005), cost-utility analysis should not be the sole basis for decisions on cost-effectiveness. There are a number of factors in addition to the variability of dosing that justify the acceptability of lapatinib plus capecitabine compared to trastuzumab-containing therapies at ICERs between £20,000 and £30,000/QALY.

The valuations of health states have been obtained from the general UK population without reference to the disease context. There is an argument that patients (and perhaps the general public) place a higher value on a QALY gained from 'extra' time towards the end of a life that is being 'cut short' than a QALY gained elsewhere (such as a small increase in quality of life over a long period of time). Empirical evidence suggests that people are willing to sacrifice quality of life gains in order to give priority to the most severely ill and that the shorter someone's life expectancy, the higher the social value of increased survival. (Dolan 2005; Dolan 2006). Therefore, the full benefit to patients of lapatinib plus capecitabine may not be fully represented in the cost/QALY estimates.

Lapatinib is expected to be the first therapy licensed and proven for use specifically in HER2+ patients who have progressed on or following trastuzmab. The population likely to receive the technology currently have no licensed alternative for HER2+ suppression. Principle 11 of NICE's Social Value Judgments (NICE 2005) states that whilst not promoting the use of interventions that are clinically/and/or cost-effective, it is recognised that individual choice is important for the NHS and its users. As an all-oral combination lapatinib plus capecitabine may be preferred over IV therapy by patients because of quality of life benefits. Wider societal benefits may be possible through the effects on carers of reduced burden of hospital attendance and/or time required for medication administration.

In addition, resource use in oncology units may be lower for lapatinib plus capecitabine versus IV therapies, particularly within pharmacies and for those involved in drug delivery. These issues are discussed further in Section 7.7-7.9.

As discussed in Section 4.2, lapatinib has a unique mode of action and, in combination with capecitabine, provides a new and innovative option for continued HER2-suppression in patients who have progressed on a trastuzumab-based regimen.

For patients who would currently be continued on a trastuzumab regimen beyond progression, lapatinib plus capecitabine is a cost-effective alternative. Examples of patients who may be suitable for continued trastuzumab include those with: stable disease at most sites with progression at an isolated site, few metastases in the soft tissues or bone and a previous good response to trastuzumab. These patients represent a group for whom lapatinib plus capecitabine should be recommended as a cost-effective use of NHS resources.

6.3.4.1. Are the results from this economic evaluation consistent with the published economic literature?

If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The systematic review of cost-effectiveness did not identify any economic evaluations of lapatinib in the treatment of metastatic breast cancer. Consequently, there is no basis for comparison of results against other published studies.

6.3.4.2. Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The economic evaluation is based on efficacy data from two sources, the EGF100151 trial and data from studies of trastuzumab continued beyond progression. The licence for lapatinib is expected to reflect the population of patients eligible for the EGF100151 trial and therefore the economic evaluations based on this trial data are expected to be broadly representative of those patients who could use the technology. Although the license may be permissive regarding the disease setting in which the prior trastuzumab is given, this submission and the EGF100151 trial are restricted to consideration of those patients who have already received trastuzumab in the metastatic setting.

As discussed in section 5.9.1, patients who may be more suitable for continuing trastuzumab therapy in the absence of an alternative HER2-suppressing agent are largely represented within data sources used for estimates of treatment effectiveness, and this evaluation is therefore relevant to them.

As mentioned in section 6.2.2.3, patients with brain metastases constitute an obvious sub-group. However, patients with progressive brain metastases were excluded from EGF100151, and the number enrolled with stable brain metastases was very small Whilst these patients are likely to be represented in the pooled evidence provided for trastuzumab beyond progression it was not possible to extract data for this sub-group in order to perform specific sub-group analysis. It is important, however, to note that in study EGF100151 lapatinib plus capecitabine reduced the incidence of first relapse within the CNS compared with single-agent capecitabine (p=0.0445), suggesting a level of preventative action regarding brain metastases. Additionally, in a phase II study some partial clinical responses or extended stable disease were seen in patients receiving lapatinib monotherapy who had progressive brain metastases following trastuzumab therapy (NCI CTEP 6969).

6.3.4.3. What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The key strengths and weaknesses of the economic analysis of lapatinib plus capecitabine is presented below.

Key strengths

- The scope of the economic analysis is comprehensive and includes all relevant treatment options.
- Use of transparent previously established framework to evaluate costs and effects of metastatic breast cancer. (Tappenden 2006a; Tappenden 2006b)
- The structure of the model is clinically appropriate and makes the most of the available data from the EGF100151 study.

- Few modelling assumptions are required to model the clinical benefits of lapatinib plus capecitabine versus capecitabine.
- The use of EQ-5D utilities, valued using the tariffs reported by Dolan (Dolan 1997) is consistent with NICE's Reference Case.
- Cost estimates are taken from internally consistent sources (Remak 2004)
- The sensitivity analysis is comprehensive in scope and allows for all uncertainty surrounding the incremental cost-effectiveness of lapatinib plus capecitabine.
- The submission model has been externally and independently reproduced by Oxford Outcomes Ltd.

Key weaknesses

- The key weaknesses of the economic analysis surround the availability of evidence rather than the methods employed.
- There is limited evidence concerning the effectiveness of single-agent vinorelbine and trastuzumab-containing regimens in the treatment of women with metastatic breast cancer whose tumours overexpress HER2 and who have received prior therapy including trastuzumab, an anthracycline and a taxane. Consequently, the relative effectiveness of trastuzumab-containing therapies was modelled using indirect comparisons, whilst relative effectiveness of vinorelbine monotherapy was modelled based on an assumption of equivalence to capecitabine monotherapy.
- Similarly, evidence concerning dose intensity was not available for single-agent vinorelbine and trastuzumab-containing regimens, hence the analysis was based on assumptions using data from the EGF100151 study.
- The model does not capture the cost or quality of life impact of adverse events resulting from the use of the specific treatment regimens. This exclusion from the base case analysis was due to a lack of evidence. The cost impact of adverse events has been addressed within the sensitivity analysis.
- Due to limited reporting in the source data, many of the standard errors used within the sensitivity analysis were based on assumptions.

6.3.4.4. What further analyses could be undertaken to enhance the robustness/completeness of the results?

The sensitivity analysis presented within this submission is broad in scope and covers all key areas of parametric, structural and methodological uncertainty. The collection of further evidence concerning the relative benefits and costs of lapatinib plus capecitabine as compared against vinorelbine and trastuzumab-containing options would clearly be of value.

7. Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document 'Guide to the methods of technology appraisal'.

7.1. What is the estimated annual budget impact for the NHS in England and Wales?

IMS market research data were used to estimate the proportion of patients receiving capecitabine, vinorelbine and trastuzumab-containing regimens (see Appendix 9.4). The per patient lifetime treatment cost for each treatment strategy (including VAT for drug acquisition costs) was calculated using the cost-effectiveness model described in Section 6. This cost was then multiplied by the number of patients assumed to receive the regimen in England and Wales to give an overall estimate of the budget impact of currently used treatments (See Table 7.1).

Table 7.1 Estimated current cost of treating HER2+ metastatic breast cancer following progression on trastuzumab (excluding lapatinib)

Treatment option	Percentage of patients	Number of new eligible patients per year	Lifetime treatment cost	Estimated cost
Capecitabine monotherapy	48.7%	800	£12,185	£9,750,782
Vinorelbine monotherapy	8.9%	146	£14,615	£2,137,397
Trastuzumab plus vinorelbine	17.7%	291	£32,527	£9,460,278
Trastuzumab plus capecitabine	17.7%	291	£30,106	£8,756,286
Trastuzumab monotherapy	7.0%	115	£28,662	£3,296,789
Lapatinib plus capecitabine	0%	0	£28,149	£0
Total	**100%**	**1643**	**-**	**£33,401,532**

Currently, the lifetime cost of treating women with HER2+ metastatic breast cancer following progression on trastuzumab is estimated to be approximately £33.4 million.

In calculating the budget impact, some simplifying assumptions have been made:

- The lifetime treatment cost has been used to calculate an annual budget estimate assuming a steady state of metastatic breast cancer (no increase or decrease in cases developing the condition).
- Lifetime treatment costs are assumed to occur within the year of patient eligibility for treatment with lapatinib plus capecitabine rather than spread over the lifetime of the patient. This is expected to result in the budget impact model showing higher than actual costs in initial years. However, as median survival for patients in EGF100151 (at 03 April 2006 cut off) was approximately 67 weeks this effect is not expected to be significant.

Tables 7.2 and 7.3 show the projected total costs of treating women with HER2+ metastatic breast cancer following progression on trastuzumab after the introduction of the lapatinib plus capecitabine regimen over a 5-year period. For illustrative

purposes this analysis assumes a linear annual increase in uptake of 10 percentage points for lapatinib plus capecitabine. Table 7.1 (Scenario A) assumes lapatinib plus capecitabine replaces all therapies proportionately. Table 7.2 (Scenario B) assumes lapatinib plus capecitabine replaces only trastuzumab-based regimens.

Table 7.2 Projected total costs of treating HER2+ metastatic breast cancer following progression on trastuzumab after the introduction of lapatinib (when lapatinib plus capecitabine replaces all current regimens equally - Scenario A)

Treatment regimen	Year 0 (0%)	Year 1 (10%)	Year 2 (20%)	Year 3 (30%)	Year 4 (40%)	Year 5 (50%)
Capecitabine monotherapy	£9,750,782	£8,775,704	£7,800,625	£6,825,547	£5,850,469	£4,875,391
Vinorelbine monotherapy	£2,137,397	£1,923,657	£1,709,918	£1,496,178	£1,282,438	£1,068,699
Trastuzumab plus vinorelbine	£9,460,278	£8,514,250	£7,568,222	£6,622,195	£5,676,167	£4,730,139
Trastuzumab plus capecitabine	£8,756,286	£7,880,658	£7,005,029	£6,129,400	£5,253,772	£4,378,143
Trastuzumab monotherapy	£3,296,789	£2,967,110	£2,637,431	£2,307,752	£1,978,073	£1,648,394
Lapatinib plus capecitabine	£0	£4,625,494	£9,250,988	£13,876,483	£18,501,977	£23,127,471
Estimated total cost	**£33,401,532**	**£34,686,873**	**£35,972,214**	**£37,257,555**	**£38,542,896**	**£39,828,237**
Additional budget cost	£0	**£1,285,341**	**£2,570,682**	**£3,856,023**	**£5,141,364**	**£6,426,705**

Table 7.3 Projected total costs of treating HER2+ metastatic breast cancer following progression on trastuzumab after the introduction of lapatinib (when lapatinib plus capecitabine replaces only trastuzumab-based regimens - Scenario B)

Treatment regimen	Year 0 (0%)	Year 1 (10%)	Year 2 (20%)	Year 3 (30%)	Year 4 (40%)	Year 5 (50%)
Capecitabine monotherapy	*£9,750,782*	*£9,750,782*	*£9,750,782*	*£9,750,782*	*£9,750,782*	*£9,750,782*
Vinorelbine monotherapy	*£2,137,397*	*£2,137,397*	*£2,137,397*	*£2,137,397*	*£2,137,397*	*£2,137,397*
Trastuzumab plus vinorelbine	£9,460,278	£8,514,250	£7,568,222	£6,622,195	£5,676,167	£4,730,139
Trastuzumab plus capecitabine	£8,756,286	£7,880,658	£7,005,029	£6,129,400	£5,253,772	£4,378,143
Trastuzumab monotherapy	£3,296,789	£2,967,110	£2,637,431	£2,307,752	£1,978,073	£1,648,394
Lapatinib plus capecitabine	£0	£1,961,210	£3,922,419	£5,883,629	£7,844,838	£9,806,048
Estimated total cost	**£33,401,532**	**£33,211,406**	**£33,021,281**	**£32,831,155**	**£32,641,029**	**£32,450,903**
Additional budget cost	**£0**	**-£190,126**	**-£380,252**	**-£570,377**	**-£760,503**	**-£950,629**

Table 7.2 suggests that the total additional cost of introducing lapatinib plus capecitabine for the treatment of HER2+ metastatic breast cancer following progression on trastuzumab is relatively small, starting at less than £1.3 million in the

first year, and increasing by this same amount each year until year 5. Table 7.3 illustrates that cost savings of approximately £200,000 could be made in year 1 by replacing 10% of trastuzumab-based regimens used beyond progression with lapatinib plus capecitabine. This increases to savings of close to £1 million in year 5 if 50% of current use of trastuzumab-containing regimens is replaced.

It is unclear how many patients who receive trastuzumab beyond progression are the most suitable, according to the descriptions given in Section 2.6., i.e. those in whom the drug still appears to be having some effect, despite progression. It is also important to acknowledge that the variation in clinical practice occurs and therefore that savings would be realised in centres where trastuzumab beyond progression is currently used as a treatment strategy.

7.2. What number of patients were assumed to be eligible? How was this figure derived?

The derivation of the number of patients eligible to receive lapatinib plus capecitabine is shown in Figure 7.1 and is described below.

The number of women diagnosed with breast cancer annually was reached by taking the annual incidence of breast cancer in England and Wales (38,909 cases in 2003) (Cancer Research UK 2003) and projecting to 2007 figures (year zero) by applying an annual growth of incidence of 0.9% (Decision Resources 2006).

Of the total number of patients receiving an initial diagnosis of breast cancer (40,329), 14% of these women (5,646) present with locally advanced or metastatic cancer whilst the remaining 86% (34,683) are diagnosed with early or localised breast cancer (Lewis 2002).

The model assumes that half of these will go on to develop metastatic cancer (17,341) (NICE TA no. 34). Other data suggests earlier diagnosis and better adjuvant treatment may have reduced this figure to nearer 40% (Polychronis 2005) but the 50% figure is used as a conservative assumption (increased budget impact for lapatinib plus capecitabine) for scenario A.

An estimated 68% (15,632) of patients that develop metastatic cancer receive first-line chemotherapy. The data for this estimation was obtained from a study of approximately 150 patients with metastatic breast cancer at Guy's and St Thomas' Hospital (a major cancer centre in the UK) (see Appendix 9.4.4). It is likely that the other 32% were not suitable for further treatment or decided not to continue with therapy. These data were not split by HER2 status because of the sample size. However, according to a large French epidemiological study that examined HER2 status of patients newly diagnosed with metastatic breast cancer, 29.6% (4,627) of these patients have tumours that over-express HER2 (Penault-Llorca 2005).

It is estimated that 66% of HER2+ metastatic patients (3,054) receive trastuzumab as their first-line treatment whilst the remaining 34% (1,573) of patients receive a non-trastuzumab regimen. (see Praxis data in Appendix 9.4.3)

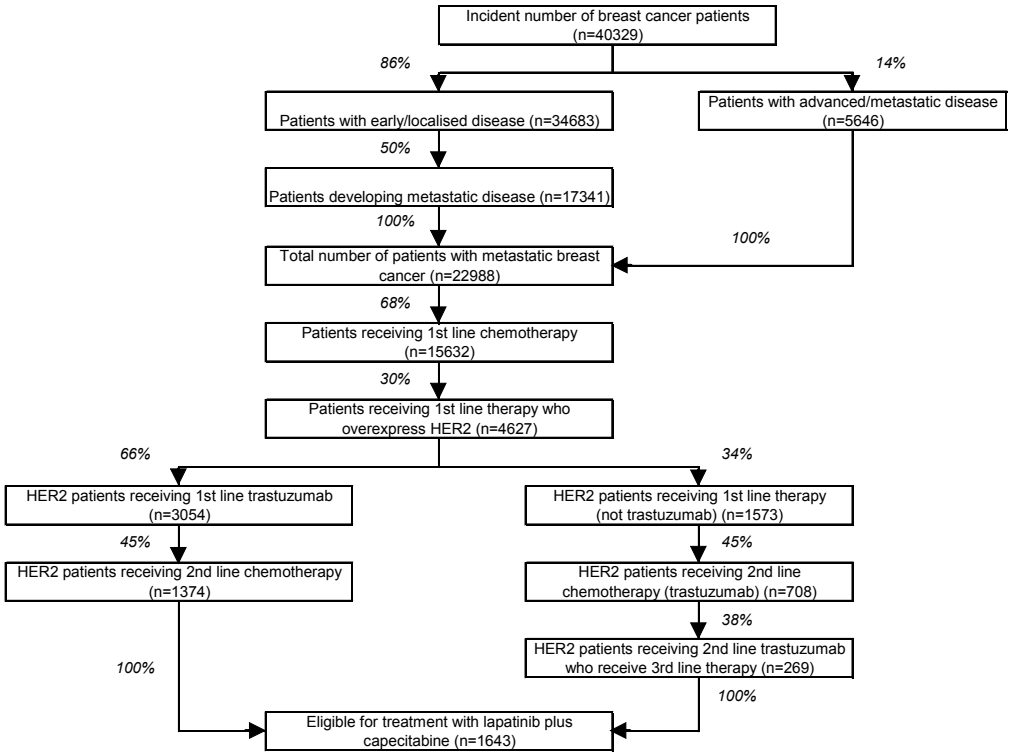
The data from Guys and St Thomas' suggests that 45% of patients receive a second-line of therapy (1,374) (see Appendix 9.4.4) and therefore those who received trastuzumab first-line (1,374) are eligible for lapatinib plus capecitabine (assuming they have previously received an anthracycline and a taxane).

It is assumed that following a non-trastuzumab first-line treatment regimen, all patients who receive a second line of therapy are prescribed trastuzumab (708). Data from Guy's and St Thomas' Hospital suggests that 38% of those patients who receive a second line of therapy continue to receive a third-line therapy (269) and are

therefore eligible for lapatinib plus capecitabine (assuming they have previously received an anthracycline and a taxane) (see Appendix 9.4.4).

Although obtained from different sources by necessity and requiring some assumptions, these data suggest that the number of women newly eligible to receive lapatinib plus capecitabine each year is approximately 1,643 (based on the population under consideration in the decision problem, with a specified requirement for trastuzumab in the metastatic setting and assuming that these patients have previously received an anthracycline and a taxane). If lapatinib plus capecitabine replaces only trastuzumab-based regimens, the relevant patient population is 697 (i.e. 42%).

Figure 7.1 Flow chart describing the number of patients eligible for treatment with lapatinib plus capecitabine



7.3. What assumption(s) were made about current treatment options and uptake of technologies?

The proportions of patients receiving each of the current treatment options were primarily estimated from an analysis of IMS data (Appendix 9.4) and are described in Table 7.1.

The analysis assumes that possible treatment options (trastuzumab, vinorelbine, capecitabine and lapatinib) will remain the same over the projected 5-year period. Scenario A assumes that lapatinib plus capecitabine will replace these regimens in equal proportion at a rate increase of 10% each year whilst Scenario B replaces only trastuzumab-based regimens.

7.4. What assumption(s) were made about market share (where relevant)?

Current market share data were based on an analysis of IMS data as described above. Market share for lapatinib plus capecitabine is assumed to reach 50% after five years.

7.5. What unit costs were assumed? How were these calculated?

The budget impact model includes estimates of lifetime costs for all six treatment strategies included in the cost-effectiveness model. A detailed description of the cost components and calculations used to estimate each one is presented in Section 6.2.6. The price of lapatinib assumed for the budget impact modelling is that used in the economic modelling (Table 6.6). VAT for drug costs was included in the budget impact model.

7.6. In addition to drug costs, consider other significant costs associated with treatment

What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve day case or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

Lapatinib plus capecitabine are administered orally and therefore do not require hospital day case or outpatient administration costs. Since only a minority of patients prescribed infusional treatments (i.e. trastuzumab or vinorelbine) receive treatment at home (requiring the presence of a nurse), homecare delivery costs have not been quantified. The majority of patients receiving infusional treatments do so in a hospital setting. This occurs at least every 3 weeks and may be as frequent as weekly depending on the dosing regimen.

It is likely that patients on all the regimens considered would have an outpatient consultation every three weeks, irrespective of the dosing regimen.

The use of resources is dependent on treatment duration which is determined by time to disease progression or death. Both the cost-effectiveness model and the budget impact analysis include cost adjustments to account for missed doses; this is handled using relative dose intensity data from study EGF100151. Costs associated with adverse events (irrespective of treatment, i.e. general for metastatic breast cancer patients) are included in both the cost-effectiveness model and the budget impact analysis. The costs of specific lapatinib-related adverse events are incorporated in the sensitivity analyses in section 6.3.3 but are not analysed in the budget impact modelling as they did not materially affect the cost-effectiveness of treatments. Data from EGF100151 show that lapatinib plus capecitabine is a well tolerated regimen with a manageable toxicity profile.

7.7. Were there any estimates of resource savings? If so, what were they?

As lapatinib plus capecitabine is given orally, uptake of this regimen will produce resource and cost savings due to the avoidance of hospital attendances and lower pharmacy preparation costs for patients previously treated with trastuzumab-containing regimens and vinorelbine. For patients receiving trastuzumab-based regimens, the cost-effectiveness model suggests that these administration and pharmacy costs will be between £5,077 and £6,466 per patient. The lifetime administration and pharmacy costs for lapatinib plus capecitabine are estimated to be around £227 per patient, which represents cost savings for administration and pharmacy preparation of between £4,850 and £6,239 per patient. Consequently, within the base case analysis, lapatinib plus capecitabine compared to trastuzumab-containing regimens is expected to produce overall cost savings.

7.8. Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The introduction of lapatinib plus capecitabine, as an oral combination regimen, has the potential to reduce the need for IV administration of chemotherapy and/or trastuzumab in the hospital setting, thereby releasing capacity for deployment elsewhere in chemotherapy services. The impact on capacity is difficult to quantify as introducing a new intervention will affect many areas within the treatment pathway, across the whole of cancer services, and not just within the area under consideration (i.e. breast). Furthermore there is enormous local variation in the organisation and implementation of cancer services, so any quantification attempted would need to take this into account.

Many Government and independent reports continue to show the extent of variations in uptake, particularly for cancer treatments which have already been approved by NICE and the SMC (National Cancer Director Reports, 2003 and 2006). As a response to this a working partnership of the Pharmaceutical Oncology Initiative Group (POI) of the Association of the British Pharmaceutical Industry (ABPI), the Cancer Action Team (CAT) of the Department of Health (DoH), and the Cancer Services Collaborative "Improvement Partnership" (CSCIP) has developed the Chemotherapy Planning Oncology Resource Tool (C-PORT) to facilitate capacity planning and allow aggregation of data from localities in order to gain a regional and National picture of chemotherapy services. C-PORT is in its infancy and has not been rolled out throughout England and Wales. Nevertheless this project highlights the NHS, DH and pharmaceutical industry commitment to improving chemotherapy services. The introduction of lapatinib as a therapeutic option supports this commitment, and it is hoped that its impact on chemotherapy capacity planning will be assessed using C-PORT when this is feasible.

7.9. Additional information on resource allocation and equity, societal or ethical issues, plus any impact on patients or carers

Patients with HER2-positive advanced or metastatic breast cancer, who progress on or following treatment with trastuzumab, represent a population with an unmet clinical need with very few therapeutic options available to them. As metastatic breast cancer is essentially incurable, effective treatment options that can delay progression or improve the likelihood of survival without negatively impacting quality of life and adding to the toxicity burden are greatly needed in this patient group. In particular, given that HER2-targeted therapy is a crucial component of treatment for patients with HER2+ disease, there is a clear need for alternative HER2-targeted therapies.

Lapatinib plus capecitabine is a treatment option that has been specifically evaluated and will be licensed for use in this setting. The clinical benefits of this treatment versus capecitabine monotherapy have been shown in the EGF100151 RCT. Lapatinib plus capecitabine provides patients with a median of approximately two months of additional progression-free time (independently assessed TTP from study EGF100151) over that expericienced by patients treated with capecitabine alone, and this may translate into prolonged survival. For these relatively young women these gains can be disproportionately valuable. The value of this additional time at the end of a patient's life is not fully represented in the cost/QALY estimates (as described in 6.3.4).

The option of lapatinib plus capecitabine may reduce the burden on patients and carers for those who would otherwise be treated with trastuzumab-based regimens. For example, visits to hospital and/or time spent receiving treatment are likely to be decreased, allowing patients and carers to gain more time for activities that might enhance the quality of their lives.

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